Cyclosporine therapy for psoriasis : how to improve the risk-benefit ratio

CYCLOSPORINE THERAPY FOR PSORIASIS

How to improve the risk-benefit ratio.

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CYCLOSPORINE THERAPY FOR PSORIASIS

How to improve the risk-benefit ratio

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Rijksuniversiteit Limburg, op gezag van de Rector Magnificus, Prof.mr. M.J. Cohen, volgens het besluit van het College van Dekanen, in het openbaar te verdedigen op donderdag 8 april 1993 om 16.00 uur

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MARINUS JAN KORSTANJE

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VOOR MIJN OUDERS

CONTENTS

ABBREVIATIONS

APC	Antigen Presenting Cell
Cock	Cockroft formula (see page 113)
Creat	Creatinine
CsA	Cyclosporine
CTL	Cytotoxic T lymphocyte
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
ERPF	Effective renal plasma flow (see page 134)
GFR	Glomerular filtration rate (see page 134)
GM-CSF	Granulocyte-macrophage colony stimulating factor
ICAM	Intercellular adhesion molecule
IL	Interleukin
IP3	Inositol 1,4,5 triphosphate
MAP	Mean arterial pressure (see page 134)
MED	Minimal effective dose
MHC	Major histocompatibility complex
MTX	Methotrexate
NS	Not significant
PASI	Psoriasis Area and Severity Index (see page 71)
RBF	Renal blood flow (see page 134)
RIA	Radio immunoassay
SCr	Serum creatinine
SD	Standard deviation
S.e.m	Standard error of the mean
TNF	Tumor Necrosis Factor
TRVR	Total renal vascular resistance (see page 134)
TxA2	Thromboxane A2
UVB	Ultraviolet B
PUVA	Psoralens + ultraviolet A
Re-PUVA	Retinoids + PUVA

PREFACE

The first part of this thesis consists of reviews of the literature about the clinical features, histopathology, and the therapeutic modalities for psoriasis. The effects of cyclosporine on the immunologic mechanisms in psoriasis and other indications for cyclosporine in the field of dermatology, other then psoriasis or atopic dermatitis, are discussed as well.
Research in psoriasis has been rapidly expanding over the past decade. Large textbooks are available about psoriasis alone and our knowledge about the pathogenesis seems never up to date. Therefore, the introduction in this thesis can not be a complete overview about every aspect of psoriasis nor a summary of the latest developments. It simply intends to give a brief impression about psoriasis and its therapies, for those who are not familiar with the disease. Without this knowledge about psoriasis it is impossible to understand the importance of cyclosporine or its important place in the therapeutic arsenal for severe psoriasis.

Part II consists of two studies and a case report. This part of the thesis is focussed on the effectiveness of cyclosporine in the treatment of psoriasis, pustular psoriasis and atopic dermatitis. We report, for the first time, that cyclosporine is highly effective for the treatment of atopic dermatitis. Atopic dermatitis is after psoriasis the most important indication for cyclosporine therapy in dermatology. Cyclosporine is one of the most potent drugs for the treatment of psoriasis and atopic dermatitis. However, its use is limited by side-effects.

In Part III the results of studies with dose regimens and combination therapies between cyclosporine and conventional therapies for psoriasis are discussed. The combination therapies were studied to find a way to improve the effectiveness of the cyclosporine therapy with diminished risk for side-effects.

The most important side-effect of cyclosporine, renal function loss, is discussed separately in Part IV. In the introduction the possible pathomechanisms for the cyclosporine induced renal function loss are discussed in a review of the available literature. Further, the accuracy of serum creatinine and the calculated creatinine clearance in relation to the golden standard, the glomerular filtration rate, is discussed. The data used in this article were obtained from our psoriasis patients, and from healthy volunteers and renal

transplant recipients treated by Dr.J.J.Homan van der Heide in Groningen. The calculated creatinine clearance (Cockroft) is propagated in the literature, but has its own limitations. The use of cyclosporine is limited by side-effects, mainly renal function loss. A search for ways to prevent renal function loss is warranted. A combination therapy with a drug that has an influence on the pathogenesis of the cyclosporine-induced renal function loss seems necessary. Fish oil, in theory, has the potential to prevent renal function loss. In our pilot-study presented in this thesis and in publications by others fish oil seems to be promising.

Continuing research is necessary to improve the cyclosporine therapy. This thesis made clear that the solution can not be found in dose-regimens or combination therapies with existing therapies for psoriasis. A combination therapy with a drug that can influence the pathogenesis of the cyclosporine-induced renal function loss is necessary. Fish oil seems to be very promising. But other interesting drugs for further research are becoming availble. This thesis is therefore no more then a short moment in a continuing process of research, further development and improvement of cyclosporine therapy and the management of psoriasis.

PART I
INTRODUCTION

PSORIASIS [1]

Psoriasis is a genetically determined chronic disease of the skin with a prevalence of 1.5% in north-west European adults. The skin lesions are characterized by the presence of sharply demarcated, dull-red scaly plaques, particularly on extensor prominences and on the scalp. The disease is variable in duration and extent. Morphological variants are common.

Psoriasis may be divided into psoriasis vulgaris, in which pustules are absent; generalized pustular psoriasis; and localized pustular psoriasis. Psoriasis vulgaris includes psoriasis vulgaris en plaque, guttate psoriasis, nummular psoriasis and flexural psoriasis. Generalized pustular psoriasis includes the von Zumbusch type and, as variants, generalized acrodermatitis continua of Hallopeau (acral type of generalized pustular psoriasis) and impetigo herpetiformis (exanthematous type of generalized pustular psoriasis). There are three types of localized pustular psoriasis: 1. "psoriasis with pustules" in which only one or a few areas of psoriasis show pustules and the tendency to develop into a generalized pustular psoriasis is not great; 2. localized acrodermatitis continua of Hallopeau, which occasionally changes into generalized acrodermatitis continua; and 3. pustular psoriasis of the palms and soles, also called pustulosis palmaris et plantaris, which occasionally is seen in association with psoriasis vulgaris. Severe exacerbations of all types of psoriasis may cause erythrodermia.

Psoriasis vulgaris

Psoriasis vulgaris en plaque is characterized by brownish red plaques predominantly on the extensor surface of knees and elbows, the scalp and in the sacral region. Psoriasis guttata describes a shower of small lesions, appearing more or less generally over the body. Nummular psoriasis describes discs and small plaques varying in size on the limbs and trunk and in flexural psoriasis the groins, axillae, submammary areas and other body folds are affected. The psoriatic lesions are sharply demarcated, dry, and usually covered with layers of silvery scales. As the scales are removed by gentle scraping, fine bleeding points usually are seen, the so called Auspitz sign. The scalp, sacral region, and extensor surfaces of the extremities are commonly involved, although, in some patients, the flexural and intertriginous areas are mainly affected. Involvement of the nails is common. In severe cases, the disease may affect the entire skin and present itself as generalized

erythrodermic psoriasis. Pustules generally are absent in psoriasis vulgaris, although pustular psoriasis of the palms and soles occasionally occurs. Rarely, one or a few areas show pustules. Also rarely, severe psoriasis vulgaris develops into generalized pustular psoriasis. Oral lesions do not occur in psoriasis vulgaris but may be seen in generalized pustular psoriasis.

Psoriatic arthritis characteristically involves the terminal interphalangeal joints, but, not frequently, the large joints are also affected, so that a clinical differentiation from rheumatoid arthritis often is impossible.

Generalized pustular psoriasis

Basically, generalized pustular psoriasis of von Zumbusch, acrodermatitis continua of Hallopeau, and impetigo herpetiformis represent the same disease process. There is considerable resemblance and overlapping in the clinical picture of these three diseases, and they share similar histologic features. They differ mainly in mode of onset and in distribution of the lesions. Clinically, all three diseases show groups of shallow pustules on an erythematous base, and all three quite frequently show oral pustules, particularly on the tongue. Sudden exacerbations in association with chills and fever occur in all three diseases, and, in the intervals between exacerbations, all three may show lesions having the clinical appearance of psoriasis.

Acrodermatitis continua of Hallopeau is the term used if the pustular eruption involves the distal portions of the hands and feet. In the localized type of acrodermatitis continua these are the only areas affected, while in the generalized type of acrodermatitis continua extensive areas of the skin are involved in addition to the distal portions of the hands and feet. On the fingers and toes, atrophy of the skin and permanent loss of the nails may occur.

Pustular psoriasis of von Zumbusch is generally diagnosed when the pustular eruption occurs in patients with preexisting psoriasis either of the plaque type or of the erythrodermic type.

Impetigo herpetiformis is diagnosed when the disease starts suddenly without any preceding lesions of psoriasis as an extensive eruption of pustules on an erythematous base. In some instances, the lesions are annular or gyrate and show a clinical resemblance to subcorneal pustular dermatosis. Annular pustular psoriasis, though usually generalized, in some instances is localized.

Localized pustular psoriasis

This may be "psoriasis with pustules", localized acrodermatitis continua of Hallopeau, localized annular pustular psoriasis or pustulosis palmaris et plantaris.

Pustulosis palmaris et plantaris, is a chronic, relapsing disorder occurring on either the palms or the soles or both. Crops of small, deep-seated pustules are seen within areas of eryhtema and scaling. In the earliest stage, the lesions may appear as vesicles or vesico-pustules. During the subsiding stage, the pustules appear as brown macules. The sites of predilection are the midpalms and thenar eminences of the hands, and the heels and insteps of the feet. In pustulosis palmaris et plantaris, in contrast to acrodermatitis continua of Hallopeau, the acral portions of the fingers and toes are spared.

HISTOPATHOLOGY [2]

Classical psoriatic lesions show marked and characteristic acanthosis of the epidermal ridges, which are evenly elongated and club-shaped at their bases, alternating with long oedematous papillae which are club-shaped at their tips. The suprapapillary plate is thinned and the epidermal surface is covered by alternating layers of hyperkeratosis and parakeratosis. Large tortuous capillaries are present in the papillary dermis and there is a slight perivascular lymphocytic infiltrate in the subpapillary dermis. Diagnostic features of active lesions include the 'Munro microabscess' and spongiform pustules. Munro microabscesses represent an accumulation of polymorphs in the stratum corneum. Mainly neutrophils migrate into the suprapapillary plate and then aggregate in the parakeratotic mould to form a microabscess. Spongiform pustules are seen beneath the parakeratotic stratum corneum and consist of small accumulations of neutrophils intermingled with the epidermal cells.

In pustular psoriasis the histologic picture is slightly different in that the spongiform pustule occurs as a macropustule and is the characteristic lesion. With increase in size of the spongiform pustules, death of the epidermal cells occurs with resulting central cavitation. At the edges a shell of thinned epidermal cells remains. Eventually there is migration of neutrophils into the horny layer such that the picture resembles that of a large Munro abscess. Otherwise the epidermal and dermal features are similar to those of psoriasis vulgaris.

AETIOLOGY

Several large population studies have demonstrated marked familial aggregation of psoriasis. The absence of spouse aggregation excludes an environmental explanation. Therefore the genetic basis of psoriasis is indisputable.[3] The mode of inheritance is not known. There is no evidence for single-gene dominant, sex-limited or sex-linked inheritance. It has been suggested that psoriasis is caused by interaction of multiple genes.

Several factors are important since they may provoke psoriasis. Psoriasis may appear 7 to 14 days after an injury, operation incision or at the site of a scratsch. It is well known that streptococcal infections, especially in the throat, may provoke acute guttate psoriasis. Sunlight is generally beneficial, but a very small minority of psoriatics are provoked by sunlight and suffer summer exacerbation in exposed skin. Drugs as e.g. antimalarials, beta-adrenergic blocking agents and lithium may exacerbate psoriasis and may even provoke a generalized exfoliative form of psoriasis. Emotional stress may be a trigger and perpetuating factor.

THERAPEUTIC POSSIBILITIES IN PSORIASIS

In the last decade the therapeutic possibilities for psoriasis have increased substantially. Few therapies are still in an experimental stage. However, the results of these therapies are promising and their use in clinical practice in the near future seems to be likely. The therapeutic possibilities including the new therapies in psoriasis are reviewed and listed below.

COAL TAR (Pix Lithantracis, Sol. Carbo Detergens)

The colour (grey-brown to black) and the unpleasant smell make this therapy not very acceptable to the patient. The effectiveness is moderate. Therefore, coal tar is not used regularly as a monotherapy for psoriasis.

Coal tar is used in combination with dithranol. An additional effect to the effect of ditranol is assumed and the irritation of the skin due to dithranol therapy may be partially prevented. However, in a recent study [4] neither an additional effect of coal tar on psoriasis nor a beneficial effect on skin irritation in dithranol therapy was found. In another study a decrease in skin irritation was observed.[5] The oxidation of dithranol is enhanced by coal tar which may reduce the skin irritation and activity of the dithranol.[6]

Coal tar is also used in combination with light therapy in the form of ultraviolet-B (UV-B) (Goeckerman therapy). Coal tar is only effective when suberythemogenic doses of UV-B are used. There is no additional effect of coal tar when erythematogenic dosis UV-B are used.[7]

Coal tar may induce phototoxic reactions, folliculitis or acne-like skin changes. Coal tar is mutagenic and induces DNA changes after application on the skin.[8] When large skin areas are treated with coal tar, cytogenitical changes in lymphocytes are detectable in blood.[9] Further, mutagenic metabolites are detectable in urine.[10] This suggests a risk of malignant changes in the skin or elsewhere in the body. In few studies the carcinogenic potency of coal tar was shown,[11] but in other studies no evidence of a carcinogenic potency was found.[12,13] In a case-control study [14] an increased risk of skin cancer was detected in the combination therapy coal tar-UVB and in the combination therapy coal tar-psoralens in combination with ultraviolet A light (PUVA).

DITHRANOL

Dithranol and related substances have been used in psoriasis for over 85 years. Dithranol was applied to the skin in a paste for 8-24 hours. In order to improve the effectiveness

this treatment was combined with a coal tar bath and exposure to ultraviolet light [15]. Such a therapeutic scheme is time consuming, difficult to accept by the patient from cosmetical point of view and can not be used out of the hospital. Therefore this therapeutic scheme has been more or less abandoned. Monotherapy with dithranol 0.3-3% applied to the skin for only 10-45 min. is just as effective.[16,17] This treatment makes sense since dithranol is effective on cellular level in very low concentrations [18] and penetrates faster in the parakeratotic stratum corneum of the psoriasis plaque than in the orthokeratotic stratum corneum of the surrounding skin.[19] After 10-45 min. a detectable amount of dithranol has penetrated and the cream may be washed off.[19] This procedure may diminish side-effects on the surrounding normal skin. However, for convenience of the patients dithranol cremes and sticks which are not washed off after application are still in use (Psoricream(R) and Psoristick(R)).

Despite accurate application on the psoriasis plaques and short-term application, a brown discoloration of surrouding skin and skin-irritation with erythema are still common.[20] There are no therapeutic measures available which may prevent these side-effects. Corticosteroids, coal tar or anti-histaminic drugs are unable to prevent or diminish skin irritation and erythema.[21,22]

TOPICAL CORTICOSTEROIDS

The topical corticosteroids are divided in four classes of potency (See table 1). The creams with topical steroids are colourless and do not smell and are therefore very well accepted by the patients. Further, these creams are simple to use and are therefore

Table 1	Classes of corticosteroidpotency
Class I	The least potent corticosteroids. They may be used in all skin areas and may be used for maintenance therapies. They are suitable for treatment of pruritis and moderate eczema.
Class II	More potent than corticosteroids from class I. Suitable for eczemas, who do not respond to corticosteroids from class I.
Class III	Potent corticosteroids. They are indicated when corticosteroids from class II are not effective. They are e.g. used in psoriasis, lichen simplex chronicus, lichen sclerosus et atrophicus, discoïde lupus erythematosus. Because of a risk of sideeffects these corticosteroids are not suitable for use in all skin areas and intermittent therapy is advisable. Their use in children should be avoided.
Class IV	Most potent corticosteroïds. They are only suitable for short term therapies in adults with therapy resistent dermatosis and with an insufficient reaction on corticosteroids of class III.

frequently prescribed. However, the side-effects have to be considered. Potent corticosteroids on the face may cause a rosacea-like dermatitis.[23] In the intertriginous areas striae distensae may be induced.[24] Penetration of corticosteroids through the skin may, after long-term use on large skin areas, induce adrenal suppression.[25] Therefore, large skin areas should only be treated for short periods. In long-term treatment with potent steroids there is a risk of skin atrophy sometimes with telangiectasia or senile purpura [26] in all skin areas. After frequent use of topical steroids the beneficial effect may fade [27] (tachyphylaxis). Intermittent application is just as effective as continuous application and may prevent tachyphylaxis.[28]

The combination therapy topical steroids with UV radiation is as effective as UV radiation alone.[29] The use of topical steroids during therapy with retinoids has no advantages compared to retinoids alone.[30]

Treatment with dithranol may be as effective as treatment with topical corticosteroids of class III.[31] Dithranol is therefore a good and safe alternative to the use of topical steroids.

VITAMIN D3 DERIVATIVES

Topical D3 derivatives have a beneficial effect on psoriasis.[32] The effect on psoriasis is comparable to the effect of class III topical steroids. Metabolites of vitamin D3 with a good effect on psoriasis and hardly any effect on the calcium metabolism have been developed.[33] This opens possibilities for a safe oral treatment. Vitamin D3 is still experimental and is not available for regular practice.

ULTRAVIOLET RADIATION

UVB

Sunlight has a beneficial effect on psoriasis. This effect is induced by ultraviolet light in the range between 280 and 315 nm.[34,35] Ultraviolet A (UVA) is, therefore, far less effective than UVB. Treatment with UVB is, when UVB doses are as high as the minimal erythema doses, as effective as treatment with psoralens in combination with UVA (PUVA).[35] The remission period after UVB therapy is the same as the remission period after PUVA.[35]

UVB has advantages over PUVA: treatment is less time-consuming, lower heat load in the cabin, no risk of phototoxic reactions during sun exposure, sunglasses are not necessary and UVB might be less carcinogenic than PUVA.[36] UVB has no side-effects beside a risk of skin burn and perhaps an increased risk for skin malignancies.

Oral retinoids have an additive effect in UVB therapy just as they have in PUVA therapy. The combination therapy oral retinoids-UVB (ReUVB) is therefore more effective than UVB alone.[37,38]

As regards light therapy in case of psoriasis UVB is the first choice. In case of an inadequate effect the therapy may be changed to PUVA. The common UVB lamps produce a broad spectrum ultraviolet light in a range between 280-350 nm, with a peak at 305 nm. Recently a new UVB lamp has been developed (Philips TL-01), which produces a small spectrum 311-312 nm ultraviolet light. This lamp is probably more effective and less carcinogenic than common UVB lamps with a broad spectrum.[39]

PUVA

By oral use of psoralens the photosensitivity of the skin can be increased. Several psoralens are suitable for use in psoriasis. Because of the good effectiveness and high concentration in the skin 8-methoxypsoralen (8-MOP) is usually used. The spectrum of action for PUVA is between 320-335 nm.[40] The shorter wavelengths in the UVA range are more effective than the longer wavelengths.[41]

Before treatment the patients skin-type is assessed. This may be used to determine the patients initial dose UVA. However, assessment of the minimal phototoxic dose (MPD) is a more effective and accurate way to determine the initial dose.[42] The possibilities in light schemes are not discussed.

An increased risk of skin malignancies, pregnancy, lactation, allergic reactions to psoralens, severe kidney- and liverfunction impairment, eye problems like cataract and other lens problems are contra-indictions for PUVA therapy. In case of photosensitive dermatoses like lupus erythematosus, porphyria cutanea tarda a.o. PUVA therapy for psoriasis is also contra-indicated.

Side-effects of PUVA on short term may be skin burns, bullae or pruritus. After use of psoralens, nausea and or headache may occur. Psoralens may deteriorate liver functions[43] Development of bullous pemphigoid during PUVA therapy has been observed.

In the long run there is an increased risk of cataract.[44] Therefore it is necessary that for 24 hours after use of psoralens sunglases are used to protect the eyes from ultraviolet.[45] In large prospective studies no increased risk of cataract was detected when sunglasses were used.[46] Control of vision by an ophthalmologist before initiating PUVA therapy and every six months thereafter is advised. Further, the risk of skin cancers, especially squamous cell carinomas, is increased.[47] However, an increased risk of skin cancer was not detected in every study [48] and probably PUVA therapy does not affect the risk of melanoma.[49]

The combination therapies dithranol-PUVA,[50] UVB-PUVA [51] and methotrexate-PUVA [52] are more effective than PUVA alone, but are hardly used. The combination with dithranol is time-consuming and may cause stains on clothes and bath. The combination with UVB does not have a higher risk of side-effects,[51] but is technically more difficult to use and is perhaps not used for that reason. The combination with methotrexate has an unacceptable risk of development of skin cancers [53] and should not be used. Cyclosporine has no additive effect in PUVA therapy.[54] This combination should not be used because of its risk of development of skin cancers.[55]

The combination therapy retinoids-PUVA (Re-PUVA) is safe and effective. With a lower cumulative dose of UVA in combination with a lower dose retinoids than should be necessary for monotherapy, a better result can be achieved.[56] This combination is therefore used regularly.

Retinoids and PUVA do not potentiate each others side-effects. Retinoids probably inhibit skin malignancies. The use of retinoids in PUVA therapy may limit the carcinogenic effect of PUVA.[56]

RETINOIDS

Retinoids are derivatives of vitamin A (retinol). They have been in use for treatment of psoriasis for over ten years. For psoriasis etretinate was used at first but later on this was replaced by acitretin. Acitretin is the active metabolite of etretinate. The effectiveness and side-effects of acitretin are not different from etretinate.[57] The initial dose is 0,5-1 mg/kg/day divided into two administrations. As soon as the psoriasis clears sufficiently, the dose will be tapered off to the minimal effective dose, which will be the maintained dose for the rest of the treatment period (6-9 months). In case the psoriasis relapses the doses may be increased temporarily.

This treatment is only effective in 60-70% of patients with psoriasis vulgaris, but better results are achieved in psoriasis with a tendency to erythrodermia [58] and pustular types of psoriasis.[59-61] An advantage is that during therapy symptoms of psoriatic arthritis decrease or disappear.[62]

Patients always observe side-effects during therapy. Mucous membranes will become drier, which my cause cheilitis, epistaxis or conjunctivitis. Due to an increased scaling of the skin on palms and soles the skin may become so thin that hand-work and walking become painful. Some patients have an itchy feeling or develop a sticky skin which may be accompanied by chills. More then 75% of the patients observe hairloss. The alopecia is reversible after discontinuation of the therapy. In rare cases retinoids may cause

changes in the form of the hairshafts, erythrodermia, rosacea, photosensitivity or intracranial hypertension.

It is recommended not to use any retinoids in patients with an abnormal liver function. During therapy a rise in ASAT, ALAT and LDH can be observed regularly, even in patients with a normal liver function. The rise in ASAT, ALAT and LDH usually settles by itself despite continuation of the therapy with retinoids.[61] There seems to be no morphological or functional effect on the liver.[63,64] In rare cases however an acute toxic hepatitis may develop, in which case immediate withdrawal of the retinoid used is necessary.[65]

During maintenance therapy more then half of the patients develop hyperlipidemia, now and then associated with increased levels of cholesterol.[66] After dose-reduction or discontinuation of the therapy the serumlevels of the lipids return spontaneously to baseline value. High levels of triglycerides are assocated with an increased risk of cardio-vascular diseases. Therefore, an in crease in serum triglycerides should be prevented. This is possible with an appropriate diet, the use of at least three gram fish oil a day [67] or in time withdrawal of the drug.

Further, hyperostosis of joints and spine may develop together with calcifications in tendons and ligaments.[68,69] It has been advised to take X-rays of cervical- and thoracic spine and of the calcaneus before starting long-term treatment with retinoids. During therapy X-rays should be taken when problems emerge. These X-rays can be compared with the X-rays taken before therapy started, which may help to find moderate changes. It does not seem necessary to take X-rays regularly. In case one feels that a regular check-up is necessary, X-rays of the lateral aspect of the calcaneous will suffice.

After years of continuous therapy an increased muscle-tone has been observed, which may cause stiffness.[70] Probably this phenomenon is caused by muscle-damage.[71]

Retinoids are teratogenic and remain in the body for a long time after discontinuation of the therapy. Therefore it is necessary that during therapy and during the period after treatment as advised by the company a reliable contraceptive is used. Retinoids may be used in children, but it must be considered that the retinoids may cause a premature closure of epiphysis.[72] This may affect the length of the child in the long run.

New retinoids are being studied. Up till now those new retinoids show no advantage in effectiveness or side-effects compared to the retinoids which are in use already.

METHOTREXATE

In the case of severe psoriasis resistant to topical therapy and ultraviolet radiation, methotrexate (MTX) may be used. Before therapy contraindications (see table 2) must be excluded. MTX is mainly excreted by the kidneys. Therefore, in case of renal impairment adjustment of the MTX dose is necessary. Concomitant medication with drugs that may interfere with MTX clearance increases the risk of side-effects. Drugs that interfere with the renal clearance of MTX are non-steroid anti-inflammatory drugs e.g. probenicid and salicylates. Drugs that raise the level of free MTX in serum are e.g. salicylates, sulfonamides, tetracyline, and phenytoin. The risk of bone-marrow depression increases when folinic acid inhibitors like e.g. trimethoprim and sulfonamides are used at the same time. The side-effects may be prevented with an intermittent use of MTX.[73] It is advisable to use MTX in a minimal effective dose. For psoriasis MTX is usually used in a dose of 7.5-30 mg once a week. MTX can be used intramuscularly or intravenously but this is uncommon. Often the MTX dose is divided in three administrations within a 36 hour period. This treatment scheme was developed to achieve maximal inhibition of the 37 hour cell-cyclus of the keratinocytes in psoriasis.[74] It was supposed that the effectiveness of MTX in psoriasis was due to an anti-proliferative effect on keratinocytes. However, it is also possible that the effect of MTX is achieved by an immunomodulatory effect.[75] In case this is true, there is no advantage in dividing the weekly dose into three administrations within 36 hours. There seems to be no difference in effectiveness between one and three administrations[76] which may support the hypothesis of an immunomodulatory effect of MTX.

Table 2
(Relative) contraindications for treatment with methotrexate

Pregnancy and lactation
Renal impairment
Impaired liver function
Active or recent hepatitis
Liver cirrhosis
Anemia, leukopenia or thrombopenia
Alcohol abusus
Active infections
Immunodeficiency

The side-effects of MTX are listed in table 3. The side-effects are, in case of a proper patient-selection, rare. However, development of serious side-effects can not be excluded, which makes regular control necessary. Especially the hepatotoxic effect of MTX with a risk of liver cirrhosis is important.[77] The risk-factors for a hepatotoxic effect are listed in table 4. There is a large difference in the risk of irreversible liver damage found in several studies.[78,79] Therefore, the exact risk is unknown. In all studies with a cumulative dose of MTX below 1,5 gram the incidence of liver cirrhosis is low. Further, the cirrhosis is in those cases usually mild and stabilizes despite continuation of therapy[78,80]. Improvement of the cirrhosis after discontinuation of therapy has been reported.[81]

Development of cirrhosis or fibrosis can not be detected by liver function tests.[82] During MTX therapy a rise in ASAT and ALAT can often be seen. This has no clinical importance. Liver fibrosis can be detected by ultrasound. It is not known whether liver fibrosis can be detected in an early stage. This method, therefore, is not suitable for exclusion of developing liver fibrosis during MTX therapy. A liver biopsy is the only reliable way to detect livercirrhosis in an early stage. In the available literature it is advised to obtain a liver biopsy after a cumulative dose of 1,5 gram.[76] The liver punction is repeated after every subsequence cumulative dose of 1,5 gram or earlier when the results of the liver histology makes it necessary. In some countries liver biopsies are also obtained before the initiation of MTX therapy.[76,81] This histology may be a reference for following biopsies. Concerning the low-incidence of liver-cirrhosis and the morbidity of liverbiopsies a lower frequency of liverbiopsies may be justified.[83]

Table 3
Side-effects wich may emerge during methotrexate therapy for psoriasis

General:
Head ache, fever and tiredness

Skin:
Pruritis, urticaria, moderate reversibel alopecia, ecchymosis, acute ulceration of psoriasis lesions.

Blood:
Leukopenia, anemia, thrombocytopenia

Gastrointestinal:
Ulcerative stomatitis, nausea, anorexia and less frequently impairment of liver function, pharyngitis, enteritis, vomiting and diarrhoe

Urogenital:
Microscopic haematuria, cystitis, reversibel oligospermia, menorrhagia, nephropathy and changes in spermatogenesis and oogenesis.

Central nervous system:
Headache, vertigo, dizziness, visual impairment and depressions

Table 4.
Risk factors for hepatotoxic side-effects during methotrexate therapy.

Alcohol abusus
Liver impairment in the patients history
Drug addiction
Diabetes mellitus
Obesitas
Concomitant use of hepatotoxic medication

MTX induces reversible changes in spermatogenesis. It may be possible that when men father children during MTX therapy this may affect the fetus.[84] Therefore, men should not father children when they are on MTX therapy or in the period up to three months after MTX was withdrawn. MTX is teratogenic and when used in the first three months of pregnancy it frequently causes an abortion.[85] It is, therefore, necessary that women of childbearing age use a reliable contraceptive while on MTX therapy. After withdrawal of MTX there is no increased risk of abortion or fetal abnormalities.[86]

Low-dose MTX rarely has a toxic effect on the lungs. In patients with high temperature, dyspnoe and a non-productive cough not only an infectious cause should be considered but also a toxic effect of MTX. MTX may cause diffuse alveolar damage[87] or interstitial pneumonitis with formation of granulomas and bronchiolitis.[88] Immediate withdrawal of MTX and treatment with high-dose corticosteroids can improve this serious side-effect.[88]
The combination therapy retinoids-MTX is effective in psoriasis but increases the risk of a hepatotoxic effect.[89]
It has been reported that topical MTX in a cream that enhances the penetration of MTX may be effective in psoriasis.[90] Further studies are necessary to confirm this report.

CYCLOSPORINE A

Cyclosporine A (CsA) is highly effective in psoriasis.[91,92] The use of CsA is hampered by side-effects.[93] The side-effects are listed in table 5. CsA is contraindicated in patients with infections, deficient immune system, renal impairment, an increased risk of malignant disease or a history with malignant diseases. There is an increased risk of skin malignancies when the patient has ever used arsenic or has a high cumulative dose UV radiation (which is the case when a patient has had multiple PUVA treatments). In these patients CsA may induce rapid development of skin malignancies, mainly squamous cell carcinomas.[55] In the case of concomitant medication which may raise the CsA blood level (e.g. erythromycine, ketoconazol) or medication with a potential nefrotoxic action (e.g. non-steroid antinflammatory drugs and aminoglycosides) the risk of CsA induced side-effects is increased. The initial dose of CsA is 3-4 mg/kg/day divided into two administrations. If there is an insufficient response the CsA dose may be increased to 5 mg/kg/day. Because of an increasing risk of side-effects higher doses should be avoi-

Table 5
Side effects during low-dose cyclosporine therapy in psoriasis. The most frequent side effects are listed first.

Renal impairment
Hypertension
Infections (bacterial and viral)
Hypertrichosis
Tremor
Rise in ASAT, ALAT and gammaGT
Gingiva hyperplasia
Nausea
Paraesthesias
Hyperuricaemia
Acne
Convulsions
Rise in serum potassium
Muscle and/or joint pains
Leukopenia
Tiredness and weakness
Depression
Increased risk for squamous cell carcinomas of the skin.

ded. As soon as there is sufficient improvement in the psoriasis, the CsA dose should be tapered off to the minimal effective dose. In case of side-effects the dose should be lowered by 25% each 2-4 weeks until the side-effects have disappeared.
An increase in serum creatinin of 30% or more is associated with an increasing risk of irreversible renal damage. In case of a rise in blood-pressure the CsA dose can be decreased or treatment with anti-hypertensive drugs may be started. However, the use of diuretics or beta-blocking drugs should be avoided.
Before initiating treatment with CsA a full physical examination should be carried out. Possible risks of malignancies should be excluded and therefore in women older then 40 years a cervical smear should be obtained. Patients with an increased risk of renal impairment should be excluded.
A creatinine clearance and serum creatinine should be obtained twice on different days before initiating the first treatment with CsA. The mean serum creatinine and creatinine clearance are the baseline for measurements of effects of CsA during therapy. During therapy serum creatinine and potassium levels are obtained every fortnight until week 12. Thereafter they are obtained monthly. The creatinine clearance is checked every three months. After 6 months it is checked once in a 6 month period. Blood pressure, liver functions, bilirubin, leukocytes with differentiation and protein in urine were checked monthly.

FUMARIC ACID

Oral therapy with monoethylfumaric acid and/or dimethylfumaric acid is effective in psoriasis.[94,95] Dimethylfumaric acid is more effective than monoethylfumaric acid.[94] Topical use of fumaric acid esters has no effect. This therapy is not used by many dermatologists because of the nefrotoxic and hepatotoxic side-effects [95,96] and contradictionary reports about its effectiveness. Common side-effects are nausea, gastric upset, diarrhoea, malaise and redness associated with paraesthesia in the face and leukopenia.[95] Renal and liver impairment are observed regularly.[94,95] Acute renal failure due to necrosis of tubuli is possible.[95,97] Therefore, regular control for side-effects is necessary. It is advisable to start with a low dose and to increase the dose weekly according to clinical effect and side-effects. In the case of a sufficient response the therapy is continued with the minimal effective dose.

CONCLUSION

Psoriasis can be treated in various ways. Mild and moderate psoriasis can be treated with various topical therapies while psoriasis of the guttata type and more severe psoriasis can be treated with ultraviolet radiation in various regimens or with oral therapy. In oral therapy the retinoids are more effective for the pustular types of psoriasis than the other available drugs, but methotrexate and cyclosporine are in no doubt the most potent drugs for plaque type psoriasis.

It is clear that the choice of the optimal therapy depends on the type of psoriasis, the area involved and the severity of the disease. Further, the choice of a therapy depends on the (relative) contraindications for each therapy which may exist in the individual patient. Therefore, it is only possible to give optimal treatment in psoriasis when there is extensive knowledge about the responsiveness of the different types of psoriasis and sufficient experience with all therapies.

The activity and severity of psoriasis can change dramatically in time and also the relative contraindication for the patient may change. Accordingly the optimal therapy varies in time. Further, an increasing risk for side-effects usually limits the use of the prescribed therapy and makes a regular shift of therapy necessary.

Because experience is so important in the treatment of psoriasis, most patients want and have to be treated by a dermatologist. Treatment by a doctor who is only able to prescribe one or two therapies (e.g. methotrexate and cyclosporine) is usually insufficient and is potentially hazardous.

EFFECTS OF CYCLOSPORINE ON IMMUNOLOGIC MECHANISMS IN PSORIASIS

The concept that circulating leukocytes might provide stimulatory signals that are critical for the development or maintenance of psoriatic lesions has been considered for some time.[98] In association with increased numbers of T cells (both activated and unactivated), increased numbers and types of antigen-presenting cells (APCs) were found in the epidermis and dermis of psoriatic lesions.[99,100] The activated T cells appeared to be producing lymphokines,[101] as evidenced by the expression of lymphokine-induced membrane molecules on lesional keratinocytes.[99,102-104] APCs found in psoriatic lesions are highly stimulatory for T cells,[99] and lymphokines released from the T cells of psoriatic lesions cause keratinocyte hyperproliferation and cause abnormal keratinocyte expression of markers also expressed in psoriatic keratinocytes.[105] These data support the concept that cellular immunologic processes are active in psoriasis in a manner that further promotes pathophysiologic mechanisms. The efficacy of cyclosporine A (CsA) in the treatment of psoriasis gave credence to the hypothesis that mechanisms such as those described might be important in maintaining a psoriatic lesion.

CYCLOSPORINE EFFECTS

Although CsA might act on several types of cells that are involved in psoriasis, on the basis of data from both in vitro and in vivo studies, it probably exerts especially potent effects on T cells. In vitro studies show that CsA blocks the increase in lymphokine messenger RNA, which occurs after triggering of the T-cell receptor for antigens [106] although the drug's action is distal to inositol 1,4,5-triphosphate (IP_3) generation, calcium mobilization, and interleukin 2 (IL-2) receptor gene induction.[107]

It has been postulated that CsA's differential effect on the triggering of T-cell genes is related to lymphokine gene promoter dependence on binding by nuclear factors that require refolding, whereas CsA-resistant genes (e.g. the IL-2 receptor gene promoter) can be activated by nuclear proteins that do not require refolding.[108] The major intra-cellular receptor for CsA is cyclophilin.[109] Because cyclophilin is a peptidyl-propyl cis-trans isomerase (rotamase)[110] it appears that CsA can block the peptide bond rotation that is required for the proper folding of proteins induced by activation of T-cell receptors. Folding may be necessary in order for nuclear proteins to bind to lymphokine gene promoter regions. Its inhibition would be a critical interruption in the amplification of immune responses.[108]

CsA's mechanisms of action in vivo are identical to those seen in vitro. However, because the drug blocks many, but not all, of the postreceptor triggering events in T cells, certain aspects of T-cell priming, proliferation, and differentiation can occur in vivo after antigen stimulation.[106] Thus, during in vivo therapy with CsA, T cells were primed and activated and differentiated from precytotoxic T lymphocytes (pre-CTL) to CTL, but were blocked from activating the lymphokine genes needed for proliferation, for amplification of immune responses, and for development of CTL effector activity. The blocking of lymphokines includes IL-2, interferon-gamma, IL-4, and granulocyte-macrophage/colonystimulating factor (GM-CSF).[111,112]

Examples of CsA-resistant T-cell activation include $CD8^+$ CTL clones,[113] and activation by the CD28 pathway.[114] CsA's ability to block T cells at the level of lymphokine production while leaving antigen-reactive cells poised to continue activation when the drug is withdrawn [106] is consistent with the findings that lymphokine-induced proteins on keratinocyte membranes disappear before T cells and macrophages disappear [115] and that remissions after withdrawal of therapy in psoriasis patients are relatively brief.

Despite its potent effects on lymphokine gene expression in vivo,[116] CsA may exert direct effects on a variety of other cells that potentially are involved in the pathogenesis of psoriasis. These include keratinocytes,[117] endothelial cells,[118] neutrophils [119] and mast cells.[120] Furthermore, although induction of monocyte IL-1, tumor necrosis factor (TNF), c myc, HLA-DR, and gamma-IP-10 is not affected by CsA,[112] the antigen-presenting activity of Langerhans cells and other APCs does appear to be sensitive to the drug.[115] When CsA is used to treat psoriasis, lymphokine-dependent events are blocked, although direct keratinocyte antiproliferative events are not likely to occur at achievable in vivo concentrations. The level of residual psoriasis appears to be closely linked to the presence of a macrophage whose antigen-presenting activity appears to be resistant to CsA. Additional effects are likely, but more direct data are needed to determine CsA's effect on mast cells, neutrophils, or endothelial cells in psoriasis patients.

CYCLOSPORINE EFFECTS IN PSORIASIS

T cells

Early histologic changes that occur during development of psoriasis lesions involve alterations in blood vessels and the appearance of mononuclear cells, primarily T lymphocytes and macrophage-related cells.[100,115] Although the lesions contain $CD8^+$ (suppressor or cytotoxic) T lymphocytes[100] the T cells are composed predominantly of $CD4^+$ helper or recall antigen-reactive memory T cells.[100,121,122] In psoriatic skin, a large

proportion of these $CD4^+$ cells may be recruited in a non-antigen-specific manner via specialized molecules on endothelial cells in psoriatic skin.[103] Even so, a subset appears to undergo specific activation within the lesions. Lesional T-cell HLA-DR expression,[100] IL-2 receptor expression[104] and entry into cell cycle or proliferation[122] indicate that a subset of T cells may be able to recognize antigen bound within class II major histocompatibility complex (MHC)(HLA-DR) molecules on APCs in psoriatic skin.[122]

CsA treatment of psoriasis patients causes a reduction in the density of all T-cell subsets in both the dermis and epidermis of lesions.[100,123] Decreased numbers of cells staining with the antibody to the IL-2 receptor seem to indicate that the drug has a selective effect on the IL-2 receptor positive, $CD3^+$ T cells during treatment.[123]

Activated T-cell production of lymphokines such as interferon-gamma,[101] in psoriatic lesions is the presumed mechanism by which keratinocytes abnormally express the molecules HLA-DR, ICAM-1, gamma-IP-10, OKM5, and CDw60.[99,103-105,124] The expression of these markers can be interpreted as an in vivo bioassay of lymphokine release in the lesional milieu. An early and dramatic effect of Csa treatment of psoriasis is the rapid disappearance of interferon-gamma-inducible proteins on the surface of psoriatic keratinocytes.[115]

Multiple populations of T cells are present in lesional psoriatic skin and these have various patterns of lymphokine production.[105] Consequently, other lymphokines besides interferon-gamma may be reduced by CsA. Because preliminary results indicate that T-cell lymphokines can induce keratinocyte proliferation directly[125] a driving force for keratinocyte proliferation would be removed during CsA therapy.

Antigen-presenting cells

Both Langerhans cells and non-Langerhans APCs are present in the dermis and epidermis of patients with psoriasis. Moreover, Langerhans cell distribution and morphology are somewhat altered in psoriatic epidermis.[100,126] Whereas $CD1^+DR^+$ Langerhans cells are the primary immunologic cell type in normal human epidermis,[127] a population of $CD1^-DR^+$ leukocytes are found in psoriatic epidermis. Some of these appear to be macrophages and some seem to represent CD^- cells expressing Birbeck granules.[128]

The abnormal $CD1^-DR^+$ cell population is responsible for the increased APC activity in psoriatic epidermis.[99] It is not yet known whether these cells are also responsible for the ability of epidermal cells from lesional psoriatic skin to activate autologous T cells from blood[129] or lesional skin. After CsA therapy, APC activity is altered in the skin. After 7 days of therapy, antigen-presenting activity was virtually eradicated in clinically unin-

volved skin in which Langerhans cells were the primary APCs.[115] But Langerhans cells in lesional epidermis contribute only minimally to the antigen presenting activity,[99] and therefore their inactivation would cause little change in the APC activity of lesional epidermis. Consistent with this hypothesis is the fact that antigen-presenting activity of lesional epidermis was only partly reduced at 7 days. Numbers of the abnormal APC population (non-Langerhans cell $CD1^-DR^+$ leukocytes) showed a similar partial decrease at 7 days and their loss progressed with further therapy. The numbers of these cells correlate with the level of APC activity. Their numbers also correlate closely with the improvement in severity scores.[115] Thus there appears to be a population of non-Langerhans cell CD^-DR^+ macrophages whose APC function, relative to Langerhans cells, is resistant to CsA. However, the progressive decline in their population during therapy indicates that their presence in the epidermis may depend on continued recruitment by T-cell lymphokines, which are inhibited by CsA therapy. Moreover, their close correlation with lesional severity scores indicates that their presence and activity are closely linked to mechanisms of lesion maintenance.

Keratinocytes

The question of whether CsA also has a direct effect on keratinocyte proliferation is controversial.[117,123] CsA may not have a major clinical antiproliferative effect on keratinocytes because the intracellular drug concentration needed to inhibit human keratinocyte proliferation may not be achievable in vivo during psoriasis therapy. During CsA treatment of psoriasis patients, no change was noted in keratinocyte epidermal growth factor receptor levels.[123]

INDICATIONS FOR CYCLOSPORINE OTHER THEN PSORIASIS AND ATOPIC DERMATITIS.

The efficacy of oral cyclosporine A (CsA) for the treatment of psoriasis and atopic dermatitis has been demonstrated in several studies.[130-132] However, oral cyclosporine has been used in the treatment of several different dermatoses. This article reviews a profile of dermatoses (other then psoriasis or atopic dermatitis) in which CsA therapy has been used. These dermatoses can be categorized according to their responsiveness to CsA therapy. This classification, however, should be considered provisional inasmuch as the data on CsA treatment are derived mostly from single case reports or small series of cases that may be biased.

DISEASES WITH EXCELLENT RESPONSIVENESS TO CYCLOSPORINE

Pyoderma Gangrenosum

There have been reported cases of patients with pyoderma gangrenosum, refractory to other therapy, who have been treated with CsA. Most of these patients demonstrated a marked response[133,134] to CsA in doses of 6 to 10 mg/kg/day. A maintenance dose of CsA 3 to 4 mg/kg/day is often sufficient and even long-term remission without any therapy after the lesions had been healed with CsA has been reported.[135] This indicate that CsA is useful in the treatment of patients with refractory pyoderma gangrenosum and suggest an immune mechanism in the pathogenesis of this disorder.

Behçet's Disease

The beneficial effect of systemic CsA, 5 to 10 mg/kg/day, on the ocular complications of Behçet's disease has been well documented.[136,137] Coincidental improvement of mucocutaneous and musculoskeletal manifestations has been observed in several reports.[138,139] CsA, 5 to 10 mg/kg/day, is superior in its ability to alleviate ocular disease compared with either corticosteroids or chlorambucil. However, corticosteroids and chlorambucil permitted better control of the extraocular manifestations,[140] but CsA was found to be superior to colchicine in the treatment of both ocular and extraocular disease.[141] Long-term maintenance therapy is required because the disease relapses when the drug is discontinued.

Epidermolysis Bullosa Acquisita

All reported cases of patients treated with oral CsA (6 to 9 mg/kg/day) improved within weeks of starting cyclosporine therapy.[142,143] CsA is also effective in cases of epider-

molysis bullosa acquisita that have previously been refractory to other therapies, including corticosteroids, gold, dapsone, isotretinoin, azathioprine, cyclophosphamide, and methotrexate. In conjunction with corticosteroids, the addition of CsA makes a significant reduction in the dose of corticosteroids possible.

In Epidermolysis Bullosa Acquisita there may be T-cell dependent autoantobodies to type VII collagen in the basement membrane zone.[143] CsA may inhibit the activation of immune cells resulting from autoantibody binding to tissue.

Lichen Planus

Complete clearing of severe cutaneous lichen planus after 8 weeks of therapy with oral CsA, 6 mg/kg/day, has been reported in several patients.[144,145] After cessation of CsA, some patients relapse after 3 to 4 weeks but others remain in remission.[145]

Erosive oral lichen planus showed significant healing with topical CsA.[146,147] No significant systemic absorption or side effect was reported.

Pityriasis Lichenoides Chronica

In one case report a good response to CsA has been observed. The response may be explained by an inhibitory effect on the activation of helper/inducer T cells and subsequent production of inflammatory lymphokines.

DISEASES WITH MODERATE RESPONSIVENESS TO CYCLOSPORINE

Alopecia

Oral therapy with CsA in a dose above 6 mg/kg/day is effective in the treatment of severe alopecia areata.[148] However, marked hair loss occurres within 3 months after discontinuation of CsA. Topical cyclosporine has been used with mixed results. In the most recent studies topical CsA seems not effective.[149]

In two patients with androgentic alopecia who received oral CsA, 7.5 mg/kg/day) for psoriasis, hair regrowth was observed.[150] However, the side-effects of CsA maintenance therapy limits or prevents therapy with CsA for alopecia. The mechanism of action of CsA on hair growth is unknown.

Chronic Photodermatoses

Persistent light reaction and actinic reticuloid are characterized by severe photosensitivity and dermal lymphocytic infiltrates. In dosages of 2.5 to 6.0 mg/kg/day, CsA has been

effecitive in inducing remissions in these conditions.[151,152] On discontinuation of CsA, the dermatoses promptly relapse.
Development of pseudolymphoma and malignant T-cell lymphoma during csA therapy has been reported in a patient with actinic reticuloid.[153] Since CsA may induce lymphoma's and may enhance growth of several malignancies the use of CsA in potentially premalignant conditons is potentially dangerous.

Pemphigus Vulgaris
CsA in a dose of at least 5 mg/kg/day is able to induce rapid improvement in Pemphigus Vulgaris.[154-156] CsA alone is usually unable to controll the disease sufficiently but the main advantage of using CsA is to allow a decrease in corticosteroid doses and to permit treating cortocosteroid-resistant pemphigus vulgaris. This effect is promptly lost once CsA therapy has been discontinued. Maintenace therapy of CsA in a dose of 3 to 6 mg/kg/day is required.

Pemphigoid
CsA is beneficial in the treatment of pemphigoid primarily as a steroid-sparing agent.[156,157] Relapses of pemphigoid occur when therapy is discontinued.

Acrodermatitis Continua of Hallopeau
Few case reports are available in which a moderate improvement during CsA tharapy has been observed. However, a CsA dose above 8 mg/kg/day is necessary. After discontinuation of CsA the disease relapse so maintenance therapy is necessary.[158] Side-effects of this maintenance dose can be expected.

Granuloma Annulare
In two patients there was moderate flattening of the lesions and decrease in erythema, although some papules still persisted after 8 weeks. No new lesions developed during therapy.

DISEASES WITH VARIABLE RESPONSES TO CYCLOSPORINE
Lupus Erythematosus
CsA has been used to treat steroid-dependent or steroid-resistant systemic lupus erythematosus. Used alone, CsA does not appear to have significant efficacy[159] but CsA is able to

allow a decrease in corticosteroid doses. CsA appears to be a more effective steroid-sparing agent than azathioprine.[160]

However, CsA may be associated with deterioration of renal function, especially in patients with preexisting lupus nephritis.[161] A possible case of CsA-induced severe relapse of systemic lupus erythematosus also has been reported.[162]

CsA has shown a mixed effect when used to treat cutaneous lupus erythematosus. Improvement in the skin lesions and the systemic manifestations was noted in three of four patients[163] but in another report no benefit was found in one patient with severe discoid lupus erythematosus.[164]

Dermatomyositis and Polymyositis

As adjunctive therapy to cortocosteroids, CsA may be beneficial in patients with juvenile dermatomyositis refractory to corticosteroids and cytotoxic agents.[165]

The response of adult dermatomyositis and polymyositis to adjunctive CsA therapy is unpredictable. Both improvement[166] and lack of improvement[167] have been reported. For these conditions, the usual dosage is 5 to 10 mg/kg/day.

Scleroderma

CsA, 4 to 10 mg/kg/day, has been used to treat scleroderma. In some patients an improvement was observed[168,169] while in others no signficant response was noted. Two patients with progressive systemic sclerosis in whom kidney failure developed within 2 months after treatment with CsA 2.5 to 5 mg/kg/day have been reported.[170] This discourages the use of CsA in patients with scleroderma.

Darier's disease

One patient with a good response and one patient with a mild response on CsA therapy has been reported. The mechanism by which CsA might have an effect in Darier's disease is not clear. There may be some degree of immune dysregulation, with defective cell-mediated immunity and abnormal lymphocyte responsiveness to T- and B-cell mitogens.[171]

Hidradenitis Suppurativa

One patient has shown a moderate response on CsA therapy. Paradoxically, the development of hidradenitis in two patients receiving CsA therapy for ocular inflammation disorders has been reported.[172] The reason for these discordant observations is unclear.

Cutaneous Sarcoidosis

Sarcoidosis is a cell-mediated response with granulomas gormed by macrophages/histiocytes interacting with T cells, particularly helper T cells and activated T cells secreting lymphokines.[173,174] CsA might be expected to be effective in these two conditions by inhibiting the activation of T cells and decreasing the subsequent lymphokine production and cellular responses. However, the results from case reports are inconsistent. There are reported cases of succesful therapy[175] and cases in which the patients did not show improvement. More patients have to be treated before any statement about the efficacy of CsA in this condition can be made.

Vitiligo

Immunologic abnormalities have been reported in vitiligo. In the peripheral blood of these patients the rnan total number of T lymphocytes and helper T cells is significantly depressed and suppressor T cells and natural killer cells are elevated compared with controls.[176] In addition, antimelanocyte antibodies may occur in vitiligo.[177] However, it is unclear if melanocyte destruction is immunologically mediated and if so, whether destruction occurs as a result of B-cell-derived autoantibodies or because of cytolytic T cells. Vitiliginous skin shows a lack of inflammatory T-cell infiltrate producing lymphokines. Therefore CsA might be expected ineffective for this disease.

In two patients a mild to moderate response with perifollicular repigmentation was observed. A third patient showed no response. Studies designed to ascertain whether CsA can inhibit or delay the progression of vitiligo are needed.

DISEASES WITH MINIMAL RESPONSE TO CYCLOSPORINE

Ichthyosis

CsA in a dose of 6 mg/kg/day was ineffective in patients with lamellar ichthyosis.[178] Some patients even show worsening of the disease.

Pityriasis Rubra Pilaris

In three patients a minimal improvement has been observed during CsA therapy while in another case report a patient did not respond.[179,180] This suggests that Pityriasis Rubra Pilaris may not be T-cell mediated or mediated by a non-CsA-sensitive T-cell population.

Cutaneous T-cell Lymphoma

Patients with mycosis fungoides or Sézary syndrome respond rapidly to CsA, 5 to 25 mg/kg/day, with marked improvement of their cutaneous symptoms.[181,182] However, clinical improvement is usually transient and patients soon experience rapid deterioration of their disease.[183,184]

As can be seen in this review, CsA is used in a rapidly increasing variety of skin disorders. In some inflammatory disorders a positive effect of CsA could be expected but in other skin disorders there were no indications whatsoever that CsA therapy could be effective. In the latter, sometimes unexpectedly CsA has some effect, but regularly no substantial effect was reported.

When new potent therapies become available, they are often used with to much enthousiasm; forgetting the (relative) contraindications, forgetting the side-effects, and use for unjustified indications. After incidents with side-effects and disappointing results in therapy for unjustified indications the enthousiastic use of the drug decreases and a rational use is established.

CsA may have important and irreversible side-effects. Therefore, experimenting with this drug on an individual bases can be hazardous. CsA should only be used in practise for well established indications and the use of CsA beyond the safety-guidelines can not be justified.

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PART II

CYCLOSPORINE THERAPY FOR PSORIASIS AND ATOPIC DERMATITIS

CHAPTER 1.

LONGTERM TREATMENT OF PSORIASIS WITH CYCLOSPORINE A: SIDE-EFFECTS, MINIMAL EFFECTIVE DOSE AND CYCLOSPORINE BLOOD LEVELS.

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ABSTRACT

Fourteen patients with psoriasis received long-term treatment with cyclosporine (CsA). Among patients there was great variability in the minimal effective CsA dose. In most patients long-term treatment was limited due to dose reductions made necessary because of side-effects. The therapeutic window for CsA seems small. CsA blood levels associated with side-effects and with the minimal effective dose are in the same range and correlation between CsA blood levels and effectiveness in psoriasis is weak. Therefore, in CsA therapy for psoriasis, without concomitant medication which may influence CsA blood levels, the measurement of CsA blood levels is not necessarily helpful in optimizing therapy or preventing side-effects.

INTRODUCTION

Recent studies have shown a beneficial effect of cyclosporine A (CsA) in patients with psoriasis.[1,2] However, the efficacy and tolerability of CsA as a long-term treatment have not been established, particularly as CsA can produce serious side-effects.[3] We carried out a long-term study to determine the safety and tolerability of CsA. In order to optimize the therapy we also analysed the relation between CsA trough blood levels and efficacy.

METHODS

Fourteen patients [nine female, five male, age range 32-70 years, mean (±s.e.m.) duration of disease 4.8 ± 1.04 years] with chronic plaque psoriasis were selected. The mean (±s.e.m.) psoriasis area and severity index (PASI)[4] was 29.3 ± 2.8. For the PASI criteria see Appendix 1. Patients with concomitant disease were excluded. Before treatment (baseline) and during CsA therapy, blood pressure, haematological and biochemical profiles were measured as well as trough (14 h after evening dose) levels of CsA in whole blood. The CsA blood levels were measured by a radio-immunoassay (RIA) method specific for CsA plus its metabolites and by a RIA method specific for CsA alone without metabolites. All patients received 5.0 mg/kg/day CsA given in two doses.

If at week 4 PASI was 25% above the baseline value or when at Week 12 PASI was 10% above baseline, the therapeutic response was judged to be a failure and the patient excluded from continuing the trial.

After Week 12 the CsA dose was reduced by 0.35 mg/kg/day at monthly intervals. The CsA dose associated with the first rise in PASI was regarded as the minimal effective CsA dose. In

Appendix 1: PASI criteria.

The PASI (Psoriasis Area and Severity Index) citeria can be used as an optimal objective measure for the severity of psoriasis in an individual case.

0.1 (Eh + IH + Dh)Ah
0.3 (Et + It + Dt)At
0.2 (Eu + Iu + Du)Au
0.4 (El + Il + Dl)Al +
Total sum = PASI

E = erythema
E0 = no erythema
E1 = slight erythema
E2 = moderate erythema
E3 = severe erythema
E4 = very severe erythema

I = infiltrate (I0 - I4 as with E)
D = desquamation (D0 - D4 as with E)

For Ah (activity head), At (activity trunc), Au (activity upper extremities), and Al (activity lower extremities) the following scores are applied:

0 = not affected
1 = up to 10% affected
2 = 10 - 30% affected
3 = 30 - 50% affected
4 = 50 - 70% affected
5 = 70 - 90% affected
6 = 90 - 100% affected

PASI-score varies between 0.0 and 72.0

order to assess the tolerability of CsA in long-term treatment we continued CsA treatment at the minimal effective dose for as long as possible. In the event of relapse (PASI 50% above baseline) the CsA dosage was increased to 5.0 mg/kg/day. After cessation of CsA treatment the patients were followed up for 3 months. The dates of appearance of the first rise in PASI, relapse and discontinuation of CsA treatment were noted.

Where there was an increase in serum creatinine of more than 30%, in serum potassium above the upper limit of normal range, in serum total bilirubin or liver enzymes of more than 100% or diastolic blood pressure above 95 mmHg on two consecutive visits, the CsA-dosage was reduced by 25%. If the abnormality was not corrected within 4 weeks, a further reduction of 25% was performed. If this again did not have the desired effect CsA was withdrawn.

RESULTS

Clearance

Eleven patients responded to therapy but three out of 14 patients were rated as failures at week 12. Nevertheless, all three had shown some improvement (See Table 1).

Table 1
Failures at week 12

PASI at baseline	% PASI reduction after 12 weeks
38.0	44.2
28.6	19.2
48.8	24.1

Side-effects

In 11 of the 14 patients the dose was reduced because of side-effects. The side-effects and the number of dose reductions are listed in Table 2.

A patient who had a history of depression 2 years previously became depressed during CsA therapy. The depression was cleared within 6 weeks after cessation of CsA therapy. One patient had joint pains affecting hands, shoulders and knees. She also felt very tired during CsA therapy. The serum urate was not increased. The joint pains and tiredness disappeared despite deterioration of the psoriasis in a 4 week period after cessation of CsA therapy. As this patient had never reported joint pains before, a relation with CsA therapy is likely.

Minimal effective dose

The minimal effective dose was found in 11 patients. The three remaining patients were all judged as treatment failures at Week 12. Due to dose reductions, three patients reached the minimal effective dose within 12 weeks. The mean ($\pm$ s.e.m.) minimal effective dose of these 11 patients was 3.0 $\pm$ 0.23 mg/kg/day (range 1.6-3.9).

Table 2 Side-effects and dose reductions

Side-effect	No.of patients	No. of dose reductions
Serum creat. 30% above baseline value	6	7
Potassium above upper limit of normal range	2	3
Bilirubin > 2x upper limit of normal range	1	-
γGT > 2x upper limit of normal range	1	-
Hypertension	2	2
Hypertrichosis	3	1
Tremor	2	-
Paraesthesia	2	-
Depression	1	-
Joint pains	1	1
Tiredness	1	1

In some patients more then one side-effect was observed and sometimes two dose-reductions were necessary to correct one side-effect

Table 3
Duration of therapy in weeks until CsA was stopped

Patient No.	Weeks
1	40
2	44
3	12
4	43
5	continued >93
6	24
7	24
8	continued >124
9	12
10	28
11	12
12	12
13	continued >112
14	64

Long term treatment

After 12 weeks, 10 patients continued the study (one patient discontinued medication for personal reasons). Three patients have continued CsA for over 2 years. The remaining seven patients relapsed after dose reduction for side-effects. After CsA was restarted in a dosage of 5.0 mg/kg/day, serious side-effects recurred rapidly and the psoriasis failed to clear within 4 weeks. CsA was therefore discontinued. In the follow-up period all side-effects disappeared completely. The duration of therapy in the weeks up to the discontinuation of CsA medication is listed in Table 3.

CsA blood levels

Mean (±s.e.m.) CsA blood levels, with and without metabolites, at Week 4 were 423 ± 83 and 163 ± 26 ng/ml respectively. Mean CsA blood levels with and without metabolites, at Week 12 were 262 ± 43 and 113 ± 16 ng/ml, respectively. No correlation was found between CsA dose and trough CsA blood level with and without metabolites at Week 4 (r=0.21 and 0.24, respectively) or at Week 12 (r=0.31 and 0.20, respectively).

No correlation existed between CsA dose and PASI reduction at Week 12 (r=0.13) nor between mean CsA dose of the first 12 weeks and PASI reduction at Week 12 (r=0.09).

Correlations between PASI reduction at Week 12 and CsA blood levels with and without metabolites were 0.10 and 0.35, respectively.

Mean CsA blood levels with and without metabolites at which serum creatinine 130% above baseline or serum potassium above the upper limit of normal occurred were 655 ± 79 ng/ml (range 255-1110) and 232 ± 24 ng/ml (range 125-340), respectively.

DISCUSSION

CsA is effective in psoriasis but among patients there appears to be a great variability in the minimal effective dose (1.6-> 5.0 mg/kg/day). No criteria are available to select patients who will respond to lower CsA doses.

The number of patients that could be maintained on CsA was low compared to the study of Griffiths et al.[5] In most patients long term treatment was limited by dose reductions which were necessary because of side-effects. The mean CsA blood level at which side-effects occurred was only slightly higher than the mean CsA blood level at the minimal effective dose. The therapeutic window for CsA is therefore probably small. We found a mean minimal effective dose of 3.5 mg/kg/day. This is only slightly lower than 4.6 mg/kg/day which caused irreversible kidney damage in transplant recipients.[6] However, these transplant recipients received relatively high doses of CsA in the immediate post-transplant period, but were maintained on about 5 mg/kg/day for months 3-12 after transplantation, without further dose reduction in the presence of reduced glomerular filtration rates. Further long-term studies are necessary to determine the safety of CsA therapy in psoriasis.

We did not observe any correlation between CsA dosage and therapeutic effect, nor was there a correlation between CsA dose and blood level. This is consistent with previous reports in renal- transplant recipients.[7] Since there is only a weak correlation between CsA blood level and therapeutic efficacy in psoriasis, blood levels cannot now be used to optimize CsA therapy in psoriasis. However, the most serious side-effect, renal dysfunction, does seem to be related to CsA concentration.[8,9]

Hence, in renal-transplant patients, regular trough CsA level estimations are strongly recommended.[7,8] The risk of renal dysfunction increases rapidly above a CsA trough blood level of 200 ng/ml without metabolites.[9,10] Most psoriasis patients have a minimal effective CsA dose below 4.0 mg/kg/day and a corresponding CsA trough blood level below 200 ng/ml. We have shown that CsA blood levels at the minimal effective dose are slightly lower than those in patients with side-effects.

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CHAPTER 2.

PUSTULAR PSORIASIS AND ACRODERMATITIS CONTINUA (HALLOPEAU) NEED HIGH DOSES OF SYSTEMIC CYCLOSPORINE A.

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The effectiveness of cyclosporine A (CsA) in severe plaque psoriasis was shown in several studies.[1-4] We present here a case of therapy resistent generalized pustular psoriasis and acrodermatitis continua in which treatment with CsA produced a reduction of the cutaneous lesions.

CASE REPORT

A 61-year-old man had suffered form generalized pustular psoriasis and acrodermatitis continua (Hallopeau) since 1985. There was no respons to topical therapy with class IV corticosteroid cremes in combination with psoralens plus ultraviolet A or in combination with topical methotrexate or oral methotrexate 15 mg once a week. In 1986 there were two periods in which diffuse erythroderma developed. The only effective therapy turned out to be prednisone 50 mg/day. Tapering off this dose resulted in exacerbation of psoriasis.

During a third period with diffuse erythroderma, oral treatment with CsA 8.0 mg/kg/day (blood CsA concentration 600 ng/ml) was started in combination with prednisone 10 mg/day. Within 3 weeks the skin was completely clear but severe nail lesions remained. Tapering off CyA to 5.0 mg/kg/day (blood CsA concentration 350 ng/ml) resulted in an exacerbation of acrodermatitis continua on fingers and toes within 2 weeks while pustular pustular psoriasis came back on hands and lower arms. With CsA 8.0 mg/kg/day the lesions cleared again except for nail lesions. Tapering off prednisone below 7.5 mg/day resulted in exacerbation of pustular psoriasis.

We concluded CsA was effective but a high dose was needed to clear the skin completely. Without prednisone the CsA dose needed would be higher. To prevent development of renal impairment due to CsA we did not increase CsA dose above 8.0 mg/kg/day.

COMMENTS

Generalised pustular psoriasis and acrodermatitis continua are serious forms of psoriasis. The management of these conditions cause many difficulties. In our patient the lesions did not respond to any form of therapy except for prednisone and CsA.

In severe plaque form psoriasis CsA 5.0 mg/kg/day is able to produce a dramatic reduction of the cutaneous lesions.[1-4] In our patient with generalized pustular psoriasis and acrodermatitis continua CsA 5.0 mg/kg/day had no effect. CsA 8.0 mg/kg/day (bloodconcentration 600 ng/ml) was able to clear skin lesions only in addition to prednisone 7.5 mg/day. For clearance of skin lesions by CsA as monotherapy a high-dose cyclosporine would be needed. Such a dose can cause renal impairment.[5]

Our findings are consistent with those of Zachariae and Thestrup-Pedersen,[6] who treated acrodermatitis continua with CsA 14 mg/kg/day reduced to 7.5 mg/kg/day. Meinardi et al[7] described a patient with generalized pustular psoriasis responsive to monotherapy CsA 12 mg/kg/day but unresponsive to CsA 5 mg/kg/day. With the dose of CsA 12 mg/kg/day renal impairment developed within a short time.

Since monotherapy CsA for generalized pustular psoriasis and acrodermatitis continua requires a CsA dose which can cause renal impairment within a short time, long-term treatment with CsA as monotherapy is not possible.

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CHAPTER 3

CYCLOSPORINE MAINTENANCE THERAPY FOR SEVERE ATOPIC DERMATITIS.

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ABSTRACT

Twelve patients with chronic severe atopic dermatitis were treated with cyclosporine A (CsA) in a dose of 5.0 mg/kg/day. All patients except one showed a good therapeutic response. After week six the CsA dose was lowered until an increase in atopic dermatitis was noticed (minimal effective dose). The minimal effective dose fluctuated with the severity of the atopic dermatitis. The mean minimal effective dose was approximately 4.0 mg/kg/day. Maintenance therapy with CsA for atopic dermatitis seems to be effective but may be hampered by side-effects in the same way as CsA therapy is hampered by side-effects in treatment of psoriasis.

INTRODUCTION

The therapeutic value of oral cyclosporine A (CsA) in atopic dermatitis has been reported.[1-2] However, atopic dermatitis flares after discontinuation of CsA.[2] Therefore, in case of chronic severe atopic dermatitis maintenance therapy with CsA seems to be necessary. We carried out an open trial to determine the minimal effective dose (MED) and effectiveness of CsA in long term treatment for atopic dermatitis.

METHODS

Six men and six women with ages ranging from 20 to 68 years were selected. They all fulfilled the diagnostic criteria for atopic dermatitis.[3] At least 30% of the total skinsurface was involved, the eczema was recalcitrant to conventional therapies and was chronic for at least a year. Topical- and systemic therapies or ultraviolet therapy had been discontinued 2 weeks prior to treatment with CsA. During CsA therapy no topical or oral concomitant medication was allowed except for non-steroid-containing emollients.

Before starting treatment (baseline) and during CsA therapy blood pressure, haematological and biochemical profiles were measured. The rule of nines was used for scoring the eczema extension. The severity of the eczema for erythema, papulae, vesiculae, xerosis, induration, excoriations, and pruritus was assessed in the face and neck, cubital fossae, hands, and back of the knees. The severity of each of these features was scored on a four-point-scale (0=none, 1=mild, 2=moderate, 3=severe). The eczema severity index was obtained by adding the numbers of each of the feature. These assessments were done at baseline, week 1, 2, 3, 4 and biweekly thereafter.

In our opinion the eczema extension score has a low correlation with the severity of the eczema. Due to e.g. a widespread erythema the eczema extension score may remain high while the patient and investigator believe that the eczema improved dramatically. Therefore we only used the eczema severity index to obtain the percentage of improvement in the eczema.

All patients received oral CsA (Sandimmune) at a dose of approximately 5.0 mg/kg/day in galenical capsules containing 25 mg or 100 mg CsA. In case of side-effects, e.g. diastolic blood pressure above 95 mmHg or rise in serum creatinine, CsA was withdrawn. After week 6 CsA dose was decreased weekly with 25 mg until progression of atopic dermatitis was observed (MED). The patients were treated with the MED as long as possible. For the patients who could be treated with a CsA dose below 5 mg/kg/day after week 6 and who were on MED for at least 8 weeks the mean MED during the last 8

weeks of CsA therapy was calculated. This mean MED of each patient was used to calculate the mean MED of the whole group of patients.

RESULTS

In all patients except one a substantial improvement of the atopic dermatitis was observed within 4 weeks. In one patient the atopic dermatitis deteriorated despite CsA therapy and CsA was withdrawn at week 3.

At week 6 atopic dermatitis was improved 75% or more in six patients and improved 50-75% in five patients according to the degree of involvement at baseline. However, xerosis remained a problem in all patients. At week 6 CsA was withdrawn in one patient because of hypertension RR 185/110 mmHg. Another patient stopped CsA because he wanted to use CsA only during exacerbations of his atopic dermatitis and not as a maintenance therapy.

The severity of the atopic dermatitis fluctuated despite CsA therapy. Therefore it was difficult to obtain the MED in the remaining nine patients. In two patients with improvement of atopic dermatitis of 55% and 60% at week 6 respectively, the atopic dermatitis deteriorated with a lower dose of CsA than 5.0 mg/kg/day. In the other seven patients the mean MED obtained was 4.06 mg/kg/day (SD .732). However, MED fluctuated with the severity of the atopic dermatitis. The average fluctuation for each patient was 0.3 mg/kg/day up or below the assessed MED. In none of the patients the fluctuation exceeded 0.5 mg/kg/day up or below the assessed MED. CsA remained effective during maintenance therapy for 19-32 weeks (mean 24 weeks).

DISCUSSION

Eleven out of twelve patients observed improvement in atopic dermatitis during CsA therapy. The MED of CsA in this group was approximately 4.0 mg/kg/day. This is higher than the MED for psoriasis.[4] The MED in patients with less severe atopic dermatitis may be lower. Long-term CsA therapy for atopic dermatitis is effective but it is likely that maintenance therapy with CsA for atopic dermatitis will be hampered by side-effects in the same way as CsA therapy for psoriasis is hampered by side-effects.[5] In our opinion in CsA therapy for atopic dermatitis the same safety guidelines as for CsA therapy of psoriasis should be followed.[6]

Since CsA is effective in atopic dermatitis it may also be used as a short-term therapy during severe exacerbations of atopic dermatitis.

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PART III

HOW TO IMPROVE THE RISK-BENEFIT RATIO OF CYCLOSPORINE THERAPY FOR PSORIASIS

CHAPTER 1.

INTRODUCTION

Therapy with cyclosporine (CsA) is restricted by side-effects especially time- and dose related nephrotoxicity and hypertension.[1] Therefore ways to improve the risk-benefit ratio of CsA therapy have to be found. Since topical therapy with CsA is not effective,[2] improvement of the risk-benefit ratio must theoretically be achieved by improvement of dose-regimens, combination therapy with another therapy for psoriasis or combination therapy with a treatment that may influence the pathogenesis of the most important side-effect(s) of CsA. Each of these possiblities is discussed below.
CsA-induced renal function loss will be discussed in part IV.

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CHAPTER 2.

DOSE-REGIMENS CYCLOSPORINE A ADMINISTRATION IN DERMATOLOGY; ONCE A DAY OR IN FRACTIONAL DOSES?

M.J. Korstanje
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INTRODUCTION

Recent studies have shown a beneficial effect of cyclosporine A (CsA) in patients with psoriasis.[2,5] However, CsA has serious side-effects, which include acute hepatotoxicity, acute and chronic nephrotoxicity, hirsutism, hypertension and toxic effects on the central nervous system.[4] Even a CsA dose of 4.6 mg/kg/day may cause chronic injury of the kidneys.[6]

Perhaps, in dermatology, it is possible to prevent side-effects with less frequent administration of CsA, while the therapeutic effect on the skin is maintained or increased. Therefore, we tried CsA administration once day.

METHODS

Patients with severe plaque-form psoriasis, resistent to conventional anti-psoriatic therapy (topical therapy including steroids, systemic therapy with retinoids, or PUVA) were selected. Patients with an increased risk for malignancy, impaired renal function (serum creatinine above 100 micromol/l), hypertension, impaired liver function, malabsorption syndrome, drug or alcohol abuse were excluded. The patients were randomly divided in two groups. Both groups had CsA therapy with the oral solution Sandimmune (100 mg/ml) for 8 weeks. Group A had 4.0 mg/kg/day CsA in one dose a day, group B had 4.0 mg/kg/day CsA divided in two doses a day. None of the patients had concomitant medication.

Clinical evaluation of psoriasis before and during therapy was carried out using the Psoriasis Area and Severity Index (PASI).[3] Full blood count, serum creatinine, serum potassium, ASAT, ALAT, gammaGT, alk. fosfatase and blood pressure were measured at weekly intervals.

RESULTS AND DISCUSSION

Except for nephrotoxicity no side-effects occurred. PASI scores and serum creatinine before and after treatment are given in Table 1.

The PASI score in group A (mean 24.9), was less than in group B (mean 30.9).

TABLE 1.
PASI scores and serum creatinine level

Patient No.	PASI Baseline	PASI red.% after 8 weeks*	Creat. at baseline	Creat. rise% after 8 weeks**
Group A				
1	35.1	11	71	65
2	28.6	6	73	16
3	19.6	64	66	66
4	20.4	13	78	23
5	20.6	4	79	59
Group B				
1	23.3	3	70	14
2	48.2	92	79	29
3	20.4	35	93	12
4	28.6	64	98	11
5	34.0	23	72	41

Baseline; PASI and creatinine two days before entering the study.

* PASI % reduction = $\frac{\text{baseline PASI - PASI week 8}}{\text{baseline PASI}} \times 100$

** Creatinine % rise = $\frac{\text{Creat.week 8 - baseline Creat.}}{\text{baseline Creat}} \times 100$

However, the reduction in the PASI score after 8 weeks in group A (19.6 %) was less than in group B (43.4 %). In all patients from both groups a rise in serum creatinine was observed. Rise in serum creatinine in group A (mean 45.8 %) was higher than in group B (mean 21.4%). Since we studied a small group of patients our results are not significant.

All our patients developed renal impairment during CsA therapy. This shows that the therapeutic window for CsA is very small. After discontinuation of CsA renal function normalised in all patients. Acute CsA nephrotoxicity is completely reversible. However, chronic CsA nephrotoxicity after long-term treatment can be irreversible. Since irreversible renal impairment may develop,[6] there is only a limited indication for CsA therapy in dermatology.

Renal function decreased more with CsA therapy in one dose a day, than with CsA therapy in two doses a day. Perhaps side-effects correlate more with CsA peak blood level than with CsA trough blood level. This may imply that no benefit can be expected from CsA administration in less than two administrations a day. CsA administration

should be divided in two or even more doses a day. Larger studies are required to confirm this observation and to find out the optimal administration of CsA.

There is a large difference in psoriasis response to CsA therapy among patients. Therefore, large studies are required to make any conclusion about effectiveness of CsA therapy on psoriasis with one dose a day versus two doses a day. Our pilot study was too small to make any conclusion about effectiveness. Recently in a study with allo- and autotransplantation of skin in rats the effectiveness of CsA administration once a day versus fractional doses was studied.[1] The results were consistent with those in our study. No difference in immunosuppressive effect was found whether CsA was given once a day or in fractional doses, however, renal function decreased most when CsA was given as a single daily dose. Thus, it may be necessary to divide CsA therapy in two or more doses a day in order to prevent side-effects. However, larger studies are required to confirm this observation.

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CHAPTER 3.

COMBINATION WITH OTHER THERAPIES FOR PSORIASIS

3.1 COMBINATION THERAPY CYCLOSPORINE A - PUVA IN PSORIASIS.

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Acta Derm Venereol (Stockh) 1990; 70: 89-90

Cyclosporine A (CsA) is effective in plaque-form psoriasis (1 fro Ref.). However, CsA has serious side-effects,[2] which limit CsA therapy in dermatology. In order to improve the risk-benefit ratio we tried a combination therapy consisting of psoralens and artificial ultraviolet A (PUVA) with CsA.

Four patients with chronic plaque-form psoriasis resistant to topical anti-psoriatics and partially responsive to PUVA or methotrexate were selected. Patients with any concomitant disease were excluded. Before initiating treatment (baseline) and during CsA therapy, haematologic parameters, serum electrolytes, liver enzymes, serum creatinine and blood pressure values were determined. Clinical evaluation of psoriasis was carried out using the psoriasis area and severity index (PASI).[3]

All patients received 5.0 mg/kg/day CsA (oral solution Sandimmun(R) 100 mg/ml) divided into two doses per day. In case of side effects the CsA dose was reduced by 25%. When the PASI had declined to 25 % from baseline or more, the CsA dose was reduced by 1.0 mg/kg/day every 4 weeks until an increase in PASI was observed. In the case of relapse (PASI score above 50% from baseline), PUVA was added. For PUVA therapy we used the same protocol as the United States Cooperative Clinical Trial Study.[4] When after 8 weeks of CsA therapy, PASI was still higher than 25 % from baseline, we regarded CsA monotherapy ineffective and PUVA was added.

RESULTS AND DISCUSSION

The results are listed in table 1 and 2. All patients required a daily CsA dose higher than 3.0 mg/kg/day and no additive effect from PUVA to CsA therapy was observed. In patients 1, 2, and 3, psoriasis exacerbated despite PUVA being added to CsA therapy. In patient no.4, combination therapy CsA-PUVA was effective. In the latter, however, after discontinuing CsA therapy, psoriasis could be controlled with PUVA alone. Therefore it is likely that only PUVA was responsible for the effect on psoriasis.

In patients treated with immunosuppressive drugs including CsA, a high incidence of cutaneous malignancies associated with sun exposure [5] has been reported. Since CsA is capable of promoting the survival and progression of UV-induced skin tumours [6] it is likely that the increased risk of cutaneous squamous cell carcinomas in PUVA therapy [7] is potentiated by CsA. Rapid growth of squamous cell carcinomas has been observed in patients treated with CsA for psoriasis.[8] Therefore, the combination therapy CsA-PUVA should be avoided until a beneficial additive effect from PUVA in CsA therapy is proven.

Table 1 Cyclosporine therapy

Pat. no.	PASI at baseline	PASI <25% [a]	Minimal effective dose	Relapse [b]
1	23.3	8	3.0	24
2	31.1	6	3.0	20
3	19.4	failure	-	
4	48.8	failure	-	

a.
Cyclosporine treatment in weeks until PASI was less than 25% from baseline value. When after 8 weeks cyclosporine therapy the PASI was still above 25% from baseline, therapy was considered a failure.

b.
Number of weeks with cyclosporine treatment until PASI became above 50% from the baseline value.

Table 2
Cyclosporine-PUVA combination therapy

Pat. no.	PASI% before PUVA therapy[a]	weeks CsA-PUVA	CsA dose	Side-effects	PASI% at the end[a]	Cumul. UVA dose J/cm²
1	54	6	3.0	-	86	5.6
2	51	8	3.0	creat.↑	68	4.9
3	69	16	5.0/3.5[b]	creat.↑↑	89	208.1
4	47	6	5.0	-	0	93.0

a. PASI in % from baseline value (see Table 1)
b. Before/after dose reduction for side-effects

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3.2 COMBINATION-THERAPY CYCLOSPORINE-A-ETRETINATE FOR PSORIASIS.

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ABSTRACT

Five patients with therapy-resistant plaque-type psoriasis were treated with cyclosporine. In cases where cyclosporine was not effective or in cases of relapse, etretinate was added. No additive therapeutic effect of etretinate was observed.

INTRODUCTION

Recent studies have shown a beneficial effect of cyclosporine A (CsA) in patients with psoriasis.[1,2] CsA has serious side-effects, which include hepatotoxicity, acute and chronic nephrotoxicity, hypertension, hirsutism and toxic effects on the central nervous system.[3] Irreversible injury of kidneys has been reported in cardiac transplantation patients on long-term, low-dose CsA therapy.[4] However, these patients received relatively high-dose cyclosporine in the immediate post-transplant period, but were maintained on about 5 mg/kg/day from 3 to 12 months after transplantation, without further dose reduction in the presence of reduced glomerular filtration rates.

Since CsA therapy in dermatology may be limited by side-effects we tried to improve the risk:benefit ratio with combination therapy CsA-etretinate.

METHODS

Patients with chronic plaque-type psoriasis resistant to conventional anti-psoriatic therapy were selected. Patients with a concomitant disease were excluded.

Before initiating treatment (baseline) and during CsA therapy, haematologic parameters, serum electrolytes, liver enzymes, serum creatinine and blood pressure were controlled. Clinical evaluation of psoriasis was carried out using the psoriasis-area-and-severity index (PASI).[5]

All patients received CsA (5.0 mg/kg/day b.i.d. oral solution Sandimmun(R) 100 mg/ml). When the PASI was reduced to less than 25% from baseline the CsA dose was lowered by 1.0 mg/kg/day every 4 weeks until an increase of PASI was observed. In the

Table 1 Cyclosporine therapy

Pat. no.	age	years with psoriasis	PASI baseline	PASI 25% [1]	relapse [2]	CsA dose at PASI↑ [3]	CsA dose at relapse [4]
1	32	14	22.1	failure	-	-	5.0
2	35	11	38.2	failure	-	-	5.0
3	52	16	48.1	6	10	4.0	4.0
4	32	4	22.1	8	14	4.0	3.0
5	45	24	23.3	8	16	3.0	3.0

1 Cyclosporine therapy (weeks) until PASI was 25% or less from baseline value. When after 8 weeks PASI was still above 25% therapy was considered ineffective (failure).

2 Cyclosporine therapy in weeks until PASI was above 50% from baseline value (relapse)

3 Cyclosporine dose (mg/kg/day) at which PASI started to increase

4 Cyclosporine dose (mg/kg/day) at relapse

Table 2 Cyclosporine-etretinate combination therapy

Pat. no.	PASI [1]	CsA dose [2]	weeks of therapy	PASI at the end	side-effects [3]	creat. % from baseline [4]
1	22.9	5.0	8	19.6	-	156
2	25.5	5.0	4	23.2	dry lips peeling of palms	121
3	24.1	4.0	6	24.0	dry lips nausea peeling of soles	119
4	13.2	3.0	4	18.6	dry lips alopecia peeling of palms	125
5	14.6	3.0	10	16.1	dry lips	121

1 PASI at the time combination therapy cyclosporine-etretinate was started

2 Cyclosporine dose (mg/kg/day) during cyclosporine-etretinate combinationtherapy

3 Side-effects other than a rise in serum creatinine

4 $\frac{\text{serum creatinine at the end of the study}}{\text{serum creatinine at baseline}} \times 100 =$ creatinine % at the end of the study

Baseline value was obtained shortly before cyclosporine monotherapy was started

case of relapse (a PASI score of more than 50% of the baseline value) etretinate (0.8 mg/kg/day b.i.d.) was added. When, after 8 weeks of CsA therapy, the PASI was still above 25% from baseline, we considered CsA monotherapy ineffective and etretinate was added.

RESULTS AND DISCUSSION.

The results are listed in Tables 1 and 2. In the patients with severe, therapy resistant, plaque-type psoriasis, CsA therapy was not effective in a dose below 4.0 mg/kg/day. Long-term treatment with CsA above 4.0 mg/kg/day may cause irreversible renal damage.[4] In all patients, serum creatinine increased, which was completely reversible after withdrawal of CsA. However, the therapeutic window for CsA therapy seems to be small.

Except for patient 1 all patients developed side-effects on etretinate therapy. However, an additive therapeutic effect of etretinate in CsA therapy was not observed. Larger studies are required to confirm our observations or to determine subpopulations of psoriasis patients in whom combination therapy with etretinate and CsA can be beneficial.

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3.3 CYCLOSPORINE A AND METHOTREXATE: A DANGEROUS COMBINATION

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Recent studies have shown a remarkable beneficial effect of cyclosporine in the treatment of patients with psoriasis.[1] However, cyclosporine has limited use in practice because of its potential severe side-effects.[2]
Methotrexate has a different mechanism of action in psoriasis. Therefore we tried to improve the risk/benefit ratio by combination therapy with cyclosporine and methotrexate.

METHODS

Patients with resistant psoriasis and without any concomitant systemic disease were selected. Before and during treatment, hematologic parameters; levels of serum electrolytes, liver enzymes, and serum creatinine; glomerular filtration rate; effective renal plasma flow; and cyclosporine trough blood levels were determined. Clinical evaluation was conducted with the Psoriasis Area and Severity Index (PASI)[3]
All patients received cyclosporine, 5.0 mg/kg/day, in two divided doses. conducted with the psoriasis area and severity index (PASI).[3]
In case of side effects the cyclosporine dosage was lowered to 3.5 mg/kg/day. If side effects persisted, the cyclosporine dosage was lowered to 2.5 mg/kg/day.

Table 1 Cyclosporine therapy

Pat. no.*	CsA therapy in weeks	Mean CsA level before DR	Mean CsA level after DR	Time of DR	Side-effects	PASI% ** before DR	PASI% ** after DR
1	8	325	-	-	-	20	-
2	16	220	160	wk 8	K^+↑	0	50
3	24	315	215,145	wk 4+8	Creat.↑	51	8,5
4	12	219	135	wk 6	Creat.↑	19	50

CsA = cyclosporine A; DR = dose-reduction(s)

* Patient 1 had generalized pustular psoriasis (von Zumbusch).
All other patients had severe plaque-form psoriasis

** Shortly before dose-reduction and before initiating combination-therapy of cyclosporien and methotrexate

Table 2 Combination therapy cyclosporine - methotrexate

Pat. no.*	CsA-MTX therapy in weeks	PASI during CsA-MTX therapy	GFR%	ERPF%	Side-effects**
1	2	0	31	53	Nausea, vomiting, ulcers on oral mucosa, leukopenia, trombocytopenia, ↑ of AST (ASAT). ALT (ALAT), LDH, creatinine and proteinuria
2	4	↑↑	-	-	Tiredness, nausea, vomiting, ulcers on oral mucosa, ↑ K^+
3	3	↑	84	88	↑ of AST (ASAT), ALT (ALAT), and creatinine
4	3	↑	67	71	↑ of AST (ASAT), ALT (ALAT), and creatinine

CsA = cyclosporine; ERPF = effective renal plasma flow; GFR = glomerular filtration rate; K^+ = serum potassium; MTX = methotrexate; ↑ = increase; ↑↑ = great increase

* In patient 1 psoriasis cleared completely, but in all other patients PASI increased

** Because all patients showed side-effects all patients were withdrawn from the study
All side-effects disppeared within 3 weeks after withdrawal of cyclosporine and methotrexate.

In case of relapse (PASI > 50% higher than baseline values) or in case of inadequate response to cyclosporine (PASI at week 8 > 25% from baseline), methotrexate was added. Methotrexate dose schedule was 2.5 mg at 12-hour intervals for a total of three doses, repeated at weekly intervals.

RESULTS

The results are listed in table 1 and 2. In all patients except for patient 1, side effects developed with cyclosporine therapy. After dose reduction, psoriasis increased in severety.

DISCUSSION

Cyclosporine is extensively metabolized in the liver, and the metabolites are excreted mostly by the liver.[4] Drugs that inhibit hepatic metabolism raise the blood concentration of cyclosporine.[4] Because hepatotoxicity is a frequent side effect of methotrexate therapy,[5] it is likely that methotrexate inhibits elimination of cyclosporine. Methotrexate is eliminated mainly by the kidneys.[6] Most (50% to 80%) is excreted unchanged.[6,7] Renal clearance of methotrexate and of its metabolite, 7-hydroxymethotrexate, is greater than the glomerular filtration rate, because of tubular secretion.[8] Acute and chronic nephro-

toxicity are the most important side effect of cyclosporine.[2] The glomerular filtration rate is reduced,[9] and tubular function is impaired.[10]

Cyclosporine and methotrexate therefore decrease one another's elimination. This can increase both methotrexate and cyclosporine blood levels and increase the risk of serious side effects. We strongly recommend that the combination not be used, even in patients with severe unresponsive psoriasis.

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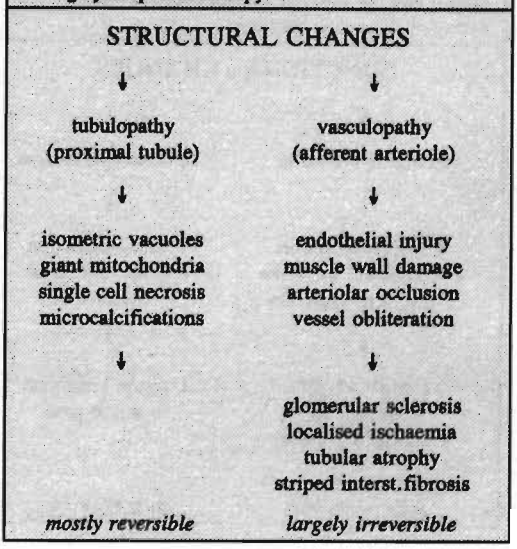
PART IV

RENAL FUNCTION LOSS AFTER CYCLOSPORINE MAINTENANCE THERAPY FOR PSORIASIS

CHAPTER 1.
INTRODUCTION

During cyclosporine (CsA) therapy there may be changes to both the tubular and the vascular system of the kidney, and these changes may be either functional or structural in nature. The changes in tubular function are common, not very important clinically, and are reversible. The changes in tubular structure are rare, occur at higher doses, and are also reversible. The changes in vascular function are common, more important clinically, but also revesibel. The changes in vascular structure, with their associated interstitial changes, are infrequent, occur at higher doses but are not reversible once established.
The renal side-effects involving structural changes to the kidney are summarized in Fig.1. The renal side-effects involving functional changes are summarized in Fig.2. The functional changes to the vessels are most noticeable as a vasoconstriction, not confined just to the kidney but also found in the systemic circulation, where they may result in hypertension. In the kidney, vasoconstriction leads to a decrease in kidney perfusion, which results in a decrease in filtration rate. The consequence of this are a rise in serum creatinine and a rise in serum urea levels. Even in the presence of established structural damage to the kidney, it is invariably the functional changes to the vessels in the form of a vasoconstriction that is responsible for renal dysfunction during CsA therapy. Only in cases of severest structural damage is the loss of functioning glomeruli responsible for a decrease in renal function. As it seems clear that the changes in renal vessel structure and function are the most important side-effects of CsA, it is important to elucidate the underlying mechanisms.
One of the earlier studies concerning mechanisms of vasoconstriction in isolated arteries concluded that CsA itself was a vasoconstrictor. This finding could not be confirmed in subsequent studies in other isolated arteries.[1,2] In addition, it

Fig.1
Description of the functional changes to the tubular system and the vascular system occuring frequently during cyclosporine therapy

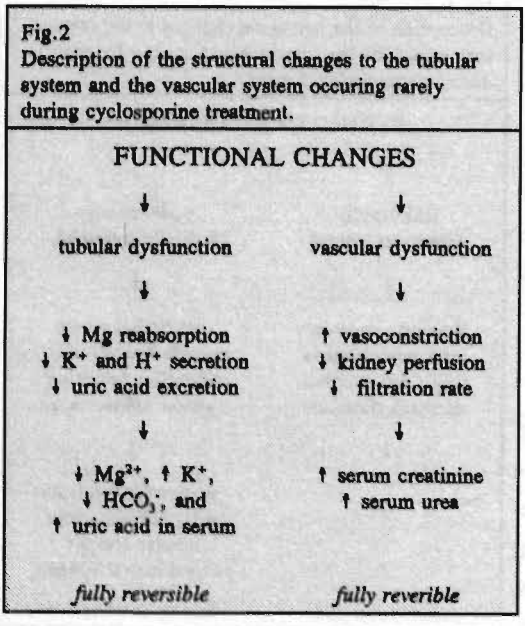


was not possible to find any binding of CsA to those receptors that cause vasoconstriction in the kidney, such as alpha-adrenergic or adenosin receptors. Also, there was almost no increase in resting intracellular Ca levels in contractile cells, with which to initiate contraction.[3-5] Therefore, the theory that CsA exerts a direct constrictory action has to be discarded.

The next mechanism that has been postulated to explain vasoconstriction is a CsA-induced increase in thromboxane and decrease in prostacyclin production. This theory was based upon the observation that thromboxane excretion is raised and prostacyclin excretion decreased in the urine of CsA-treated rats.

Another mechanism possibly involved in the generation of vasoconstriction is the action of CsA to enhance the rise in intracellular Ca seen upon stimulation with a vasoconstrictor substance. In smooth muscle cells, the calcium peak generated in response to stimulation with a vasoconstrictor substance. In smooth muscle cells, the calcium peak generated in response to stimulation with angiotensin or vasopressin is much enhanced in the presence of CsA.[3,4] This finding is also seen in glomerular mesangial cells grown in culture.[5,6] These contractile cells may, therefore, be hyperactive in the presence of CsA and contract more to any level of stimulation caused by any vasoconstrictor.

Fig.2
Description of the structural changes to the tubular system and the vascular system occuring rarely during cyclosporine treatment.



A further mechanism that may enhance vasoconstriction is the plasma volume depletion seen in CsA-treated animals.[7] When injected with radiolabeled albumin, it is apparent that the disappearance of albumin from the circulation is much higher in the CsA-treated animals than in the control animals. Hence, it seems as if the endothelium has become leaky to albumin causing plasma volume to decrease. Vasoconstriction may then partly be explained by a physiologically appropriate response to compensate for volume depletion.

A final mechanism causing vasoconstriction may be an activation of renin within the walls of renal arteries. The constrictor response of porcine renal arteries to angiotensin II does not differ in the presence or absence of CsA. However, the constrictor response to angiotensinogen, the substrate of renin, is much greater in the presence than in the absence of CsA.[8] Since the response to angiotensin I or II is not altered, the enhanced response to renin substrate suggests renin activation and increased production of angiotensin I and II. This mechanism of local renin activation and enhanced angiotensin production within the vessel wall could explain why vasoconstriction predominates in the renin-rich renal vessels.

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CHAPTER 2

ASSESSMENT OF RENAL FUNCTION AND RENAL FUNCTION CHANGES DURING CYCLOSPORINE TREATMENT

ABSTRACT

Serum creatinine (Screat), the Cockroft formula (Cock) and creatinine clearance rate are used in daily practice to assess renal function. The reliability of these assessment techniques remains questionable, however. We measured Glomerular Filtration Rate (GFR, 125I-iothalamate), Screat and Cock in 63 subjects with a normal renal function before and after cyclosporine administration (CsA) (126 paired observations, Group I) and in 50 renal transplant recipients (a total of 158 observations, up to 4 in each subject, Group II). All results were compared in the whole group with all observations combined (284) and in the separate groups (Wilcoxon and Spearman). Furthermore, changes in renal function were assessed by comparing the known pairs (Group I: 63, Group II:108, analysis of %delta change).

When combining all results, correlations were well: GFR vs Screat: $r = -0.84$, GFR versus Cock: $r = 0.93$. This was different with separate analysis: in Group I: $r = -0.22$ and $r = 0.59$, resp; in Group II: $r = -0.73$ and $r = 0.86$. With decreasing GFR, the difference between GFR and Cock increased. In Group I, GFR and Cockroft did not differ; in Group II, the difference amounted to 18.7% (-20.7 to 135.7%) ($p < 0.01$). In Group I, changes in GFR were poorly predicted by changes in Screat and Cock: %delta GFR vs %delta Screat: $r = -0.30$, vs %delta Cock: $r = 0.25$. It improved in Group II: $r = -0.67$ and $r = 0.67$, respectively.

We therefore conclude that Screat is a poor indicator of renal function in normals, and neither changes in Screat or Cock are able to accurately reflect the individual changes in GFR after CsA-administration. Despite better correlations in renal transplant recipients, Cock overrates renal function as assessed by GFR markedly under such circumstances. Changes in GFR are not adequately reflected by changes in Screat in such patients despite an apparently acceptable correlation.

INTRODUCTION

Since its introduction, cyclosporine A (CsA) is accepted as an important treatment modality in transplantation medicine.[1-3] Despite its widespread use, it also has significant side effects.[4-11] However, since advantages often outweigh disavantages with CsA after transplantation, side effects are accepted as well. One of its main side effects is a deterioration of renal function.[10,11] To assess the influence on renal function of CsA, changes in creatinine and creatinine clearance rate are used in clinical practice.

The last years do see the introduction of CsA as a treatment for other disease modalities as well.[12-16] Its use has also been advocated in diseases as diverse as insulin-dependent diabetes mellitus, inflammatory bowel diseases, uveitis, rheumatoid arthritis and multiple sclerosis. Several studies have shown a beneficial effect of CsA in patients with psoriasis or atopic dermatitis.[17-23] Such patients often have a normal renal function before the start of therapy, and CsA subsequently causes a loss of renal function, quite often leading to an adjustment or even withdrawal of CsA. After withdrawal of CsA, renal function as assessed by measurement of glomerular filtration rate (GFR), does not always return to its pretreatment values.[22] Remarkably, when only looking at serum creatinine (Screat) levels, this loss in GFR is not noted.

Cockroft and Gault advocated the use of a specific formula (implicating Screat, age, weight and sex) to calculate creatine clearance rate in order to prevent the necessity of collecting 24-hour urine samples.[23] They considered the 24-hour sampling cumbersome and often unreliable. Some consider the renal function assessment by the Cockroft approach as superior to the use of Screat.

In order to get an impression of the reliability as a tool to assess renal function and renal function changes of various methods, we performed a retrospective study of psoriasis patients, who received CsA for variable periods and dosages as treatment for severe plaque form psoriasis. Furthermore, renal transplant recipients, receiving CsA posttransplant for up to a year, were studied as well. The results of the measurements of GFR (^{125}I-iothalamate) and Screat, and Cockroft calculation were compared, both as separate values and as tools to assess the changes in renal function during CsA therapy.

METHODS

A total of 113 subjects were analyzed for this study. Sixty-three subjects participated in projects, studying the effects of cyclosporine in psoriasis patients.[18] All these subjects had a normal renal function at inclusion in any of the studies, as assessed by serum creatinine. Both at baseline and after the administration of varying doses of cyclosporine during

varying study periods, renal function studies were performed. Cyclosporine doses never exceeded 5 mg/kg in these patients.
Fifty renal transplant recipients, participating in another study were analyzed as well.[24] All patients received cyclosporine after their renal transplant and glomerular filtration rates were measured 1 month, 3 months 6 months and 12 months posttransplant.
Serum creatinine was measured concomittantly.

Renal function studies were performed with determination of the ^{125}I-iothalamate clearance for Glomerular Filtration Rate (GFR), using the formula U*V/P. The coefficient of variation of day-to-day determination of ^{125}I-iothalamate clearance amounts to 2.2%.[24] Results are expressed as ml/min and not corrected for body surface area.

Creatinine clearance rate was calculated using the Cockroft formula: [23]

$$\text{Cockroft (ml/min)} = \frac{1.23*[140-\text{Age(years)}]*\text{weight(kg)}}{\text{Screat } (\mu\text{mol/l})} \quad \text{(to be multiplied by 0,85 for women)}$$

This formula was the result of efforts to calculate the renal function as accurate as possible using the Screat. Empirical evidence showed that the best result was obtained with the 1/Screat corrected for weight and age with a correction factor of 0.85 for women. (Women have a smaller lean body mass in relation to their weight compared with men).

STATISTICAL ANALYSIS

All data are given as medians and ranges. For comparison of paired data a Wilcoxon signed rank test was used. Data were correlated using the Spearman test. A p-value of less than 0.05 was considered statistically significant.
The difference between two observations with Screat, Cock, and GFR is called delta Screat, delta Cock and delta GFR respectively. The %delta is the difference between the two observations expressed as a percentage of the first observation.
The difference between Cock versus Screat, GFR versus Screat, GFR versus Cock is called the difference Cock versus Screat, difference GFR versus Screat, and difference GFR versus Cock respectively. The %difference is the difference between the two measurements expressed as a percentage from the first measurement.
The change in the difference between two observations (eg. Cock versus Screat) is called the delta difference and can be expressed as an absolute delta difference in ml/min or as a percentage of the first observation (%delta difference).

RESULTS

The group characteristics are shown in Table 1. As can be seen, the sixty-three subjects with a normal renal function underwent renal function studies twice, allowing the analysis of changes in renal function in 63 pairs. In the renal transplant recipients, 50 subjects were analysed one month post-transplant, 48 three months post-transplant, 43 six months and 17 twelve months post-transplant, allowing the analysis of changes in renal function in 108 paired observations (48 one versus three months, 43 three versus six months, and 17 six versus twelve months).

Table 1 Group characteristics; medians and ranges

	Normal renal function	Renal transplant recipients
n	63	50
Baseline GFR*	113 (64-177)	40 (14-82)
Total observations	126 (a)	158 (b)
Men/female	41/22	28/22
Age (years)	37 (20-67)	44 (17-66)
Baseline weight (kg)	75 (50-138)	66,5 (46-91)

* GFR uncorrected for Body Surface Area

a 63 at baseline; 63 after cyclosporine treatment

b 50 one month post-transplantation;
48 three months post-transplantation;
43 six months post-transplantation
17 twelve months post-transplantation

When comparing the combined results of all renal function studies (126+158=284 observations), Cockroft calculation showed a substantially higher value compared to the GFR measurement: (median and ranges) %delta difference: 10.6% (-32.9 to 135.7%), absolute delta difference: 6.4 ml/min (-42.2 to 48.3 ml/min) (Table 2A). Correlation was remarkably well, r=0.9261 (Table 2B).

When analyzing the separate groups, the correlation between the GFR and the Cockroft formula was less pronounced: n=126, r=0.59. In subjects with a normal renal function, GFR and Cockroft did not differ (Table 3A-1), as opposed to the results in renal transplant recipients: the GFR and the Cockroft formula showed a %difference of 18.7% (-20.7 to 135.7%) (Table 4B-1). Correlation between GFR and Cockroft in this group was n = 158, r = 0.86. Therefore, the significant difference between GFR and Cockroft in the whole group had to be attributed to the renal transplant recipients only. When comparing GFR with the %difference between Cockroft and GFR it seems that with decreasing GFR the %difference increased (n=284, r=-0.56; n=158, r=-0.43, respectively).

There was a good correlation between GFR and Screat when analyzing all observations (n=284, r=-0.84, Table 2B). This was different when only correlating the results in subjects with normal renal function: n=126, r=-0.22 (Table 3B). In renal transplant

Table 2
Combined analysis of all results (n = 284; 126+158)

A: Comparison of all results (medians and ranges)

GFR (ml/min)	61 (14-177)
Cockroft (ml/min)	70 (21-168)
Screat (μmol/l)	109 (54-406)

Difference GFR vs Cockroft: 6.4 (-42.2 to 48.3) p<0.01

%difference GFR vs Cockroft: 10.6% (-32.9 to 135.7%)

The difference GFR versus Cock is the difference in renal function (ml/min) as measured by GFR and the Cockroft formula respectively. The %difference is the percentage of the difference between GFR and Cockroft formula expressed as a percentage of the GFR value.

B: Correlations (Spearman) between all results

GFR vs Cockroft	r = 0.93
GFR vs Screat	r = -0.84

Table 3
GFR, serum creatinine and Cockroft at baseline and after cyclosporine (CsA) administration in 63 psoriasis patients.

A-1: Separate analysis of results

	Baseline	CsA
GFR (ml/min)	113 (64-177)	95 (56-168) (p < 0.01)
%delta	-11.6% (-40.2 to 17.9%)	
Screat (μmol/l)	83 (54-104)	91 (59-149) (p < 0.01)
%delta	10.0% (-14.4 to 93.5%)	
Cockroft (ml/min)	109 (68-154)	99 (61-168) (P < 0.01)
%delta	-9.0% (-48.9 to 18.5%)	
weight (kg)	75 (50-138)	75 (72-135)

%Delta is the difference between baseline and the value after cyclosporine administration expressed as a percentage from baseline value

A-2: Correlations (Spearman)

%delta GFR vs %delta Screat	r = -0.30
%delta GFR vs %delta Cockroft	r = 0.25
%delta Screat vs %delta Cockroft	r = -0.94

B: Comparison/correlation of 126 observations

GFR vs Screat	r = -0.23
GFR vs Cockroft	r = 0.59
Cockroft vs Screat	r = -0.23

recipients, with a much larger variation in renal function, correlation between GFR and Screat amounted to n = 158, r = -0.73 (See table 4B-2). In subjects with a normal renal function, %delta GFR and %delta Cockroft did not correlate well: n = 63, r = 0.25, nor did %delta GFR versus %delta Screat: n = 63, r= -0.30. Incidentally, the %delta Cockroft and %delta Screat correlated well: n = 63, r= -0.94 (Table 3A-2).

In renal transplant recipients, GFR and Cockroft increased during the follow-up period (Table 4A). This also held true when analyzing all paired observations (n = 108, Table 4C-1). Screat did not show changes during the one year study period, nor in the paired analysis. However, despite this the %delta GFR correlated well with the %delta Screat (n = 108, r=-0.67).

Table 4
GFR, serum creatinine (Screat), Cockroft formula (Cock), and weight in renal transplant recipients 1 month, 3 months, 6 months, and 12 months posttransplantation

A: Separate analysis of results (medians and ranges)

	n	GFR	Screat	Cockroft	Weight
1 month	50	40 (14-82)	157 (77-406)	46● (21-86)	66.5 (46.4-91.0)
3 months	48	42** (19-84)	158 (90-280)	52●** (25-95)	69.9** (50.7-95.0)
6 months	43	46**# (14-85)	155 (77-271)	49●** (30-102)	71.2##** (51.4-93.5)
12 months	17	56* (26-111)	142 (87-232)	54* (26-121)	70.5##** (55.9-96.0)

GFR versus Cockroft * $P<0.05$, ** $P<0.01$: Baseline versus others; # $P<0.05$, ## $P<0.01$: 3 months versus others; @ $P<0.01$

The %delta GFR also showed a good correlation with the %delta Cockroft: n=108, r=0.67. Again, the %delta Cockroft and %delta Screat showed the best correlation: n = 108, r = -0.95.

4B-1: Combined analysis of 185 results	
GFR (ml/min)	43 (14-111)
Cockroft (ml/min)	49 (21-121)($p<0.01$)
SCreat (μmol/l)	156 (77-406)
%difference GFR vs Cock	18.7% (-20.7 to 135.7%) ($p<0.01$)
4B-2: Correlations (Spearman)	
GFR versus Screat	r =-0.73
GFR versus Cockroft	r = 0.86
Cockroft versus Screat	r =-0.74

DISCUSSION

Much discussion is going on regarding the best method to assess renal function and renal function changes in subjects with an initially normal renal function treated with relatively low doses of cyclosporine. Menter and Barker recently suggested that Screat is a poor indicator of renal function in such patients, this in contrast to GFR measurements.[25] Others either do show a better correlation between both renal function assessment techniques[26] or do want to believe us in such a better correlation.[27]

Our study in subjects with initially normal renal function does show a poor correlation between GFR as assessed by ^{125}I-iothalamate and Screat (and,incidentally, 1/Screat as well). Furthermore, although Screat rises with CsA-therapy in about the same magnitude as the decrease in GFR (Table 3A-1), the individual changes in GFR are not properly reflected by the individual changes in Screat, as shown in the poor correlation between

4C-1:
Combined analysis of all paired observations (n=108; baseline versus 3 months (n=48), 3 months versus 6 months (n=43), and 6 months versus 12 months)(n=17)(medians and ranges)

	Observation 1	Observation 2
GFR (ml/min)	42 (14 - 85)	45 (14 - 111) ($p<0.01$)
%delta	5.6% (-32.7 to 136.8%)	
Cockroft (ml/min)	49 (21-102)	52 (25-121) ($p<0.01$)
%delta	5.3% (-24.2 to 89.0%)	
Screat (μmol/l)	155 (77-406)	156 (77-282)
%delta	0.7% (-46.9 to 36.6%)	

%Delta is the difference between observation 1 and 2 expressed as % from observation 1.

C-2: Correlations (Spearman)

%delta GFR vs %delta Cockroft	r = 0.67
%delta GFR vs %delta Screat	r =-0.67
%delta Cockroft vs %delta Screat	r =-0.9

the %delta GFR and the %delta Screat (r = -0.30). Moreover, Screat does not reflect properly the sustained loss in GFR [22] which may remain after CsA treatment in psoriasis patients. This has also been confirmed in multiple sclerosis patients.[14] Again, others do want to believe us otherwise.[28]

Use of the Cockroft formula in subjects with an initially normal renal function yields a better correlation between the absolute results as compared to GFR-measurements (Table 3A-1). However, again the %delta Cock is only poorly correlated to the %delta GFR, thus also rendering it a less valuable tool to assess renal function changes in such patients.

Renal function, as assessed by ^{125}I-iothalamate, definitely improves during the first year after renal transplantation in our study population. This vast improvement from a median of 40 to a median of 56 ml/min is not reflected in changes in Screat values (Table 4A). The good correlation between %delta GFR and %delta Screat therefore does not appear to be as reassuring as can be possible.

Cockroft overestimates GFR, and rises during the year as well. However, since Screat does not change, one wonders whether this rise in Cockroft is not due to the rise in weight in our study population. Since an increase in weight in renal transplant recipients is more connected to an increase in fat and extracellular volume than to an increase in muscle mass, such a weight increase (being a 'zero-creatinine' increase) would artificially raise renal function.

Despite this, correlations between GFR on one hand and Cockroft and Screat on the other hand are well. Such apparently good correlations can be due to the same effect as shown when analyzing all results together: when including enough results at both sides of the possible renal function spectre (from very low to normal), correlation analysis will more often show a good result (renal function in our renal transplant recipients varied from 14

to 111 ml/min). Still, this cannot be an explanation for the reasonable correlation between %delta GFR, and %delta Cockroft and %delta Screat (Table 4C-2).

When comparing GFR and Cockroft in renal transplant recipients, the %difference increases with decreasing renal function. Our study cannot explain this difference. With decreasing renal function, tubular secretion of creatinine will increase. In the Cockroft formula, a decrease in Screat will lead to a higher calculated renal function. Further studies will be necessary to either confirm or refute this assumption.

We therefore conclude that Screat is a poor indicator of renal function in subjects with an initially normal renal function, and neither changes in Screat or Cock are able to accurately reflect the individual changes in GFR after CsA-administration. Despite better correlations in renal transplant recipients, Cock overrates renal function as assessed by GFR markedly under such circumstances. Changes in GFR are not adequately reflected by changes in Screat in such patients despite an apparently acceptable correlation.

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CHAPTER 3

SUSTAINED RENAL FUNCTION LOSS IN PSORIASIS PATIENTS AFTER WITHDRAWAL OF LOW-DOSE CYCLOSPORINE THERAPY

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ABSTRACT

Eight patients with psoriasis received low dose cyclosporine (CsA) treatment for an average period of 12 months (range 4-16 months). Among patients there was great variability in minimal effective CsA dose. In 50% of the patients long-term treatment was limited by dose reductions necessitated by side-effects.

A considerable impairment of renal function during csA therapy was found. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured with ^{125}I-iothalamate and ^{131}I-hippuran, respectively. Both at the end of the active treatment period (GFR-CsA and ERPF-CsA) and 4 months after withdrawal of CsA (GFR-4mo and ERPF-4mo) there was sustained renal impairment (GFR-BL = 97 (range 64-117), GFR-CsA reduction 17.8% (2.2-31.9%) [$p<0.02$], GFR-4mo reduction = 9.8% (5.5-21.5%) ml/min/1.73 m^2 ($p<0.05$ vs BL); ERPF-BL = 401 (232-607), ERPF-CsA reduction = 10.1 % (7.4-27.3%) [$p<0.05$], and ERPF-4mo reduction = 13.5% (3.0-32.9%) ml/min/1.73m^2 [$p<0.02$]. Further studies of the effects on renal function during, and after, long-term therapy for psoriasis with low-dose CsA are warranted.

INTRODUCTION

Several studies have shown a beneficial effect of cyclosporine A (CsA) in patients with psoriasis.[1,2] Subsequent withdrawal of the drug, however, often leads to reappearance of the skin lesions to the same extend as before treatment. Therefore, treatment with CsA has to be continued according to the natural course of the disease. Withdrawal of CsA or dose reductions are often necessary because of the side-effects.[3,4] It has been suggested that side-effects are completely reversible after withdrawal of CsA, but there are reports of chronic irreversible renal injury with a CsA dose as low as 4.6 mg/kg/day.[5,6] Morphological renal changes were also found in a patient treated for psoriasis with a dose of 2.5 mg/kg/day.[7]

We carried out a pilot-study with low-dose CsA for psoriasis, in order to determine whether renal impairment is completely reversible after withdrawal of CsA.

METHODS

Eight patients with chronic plaque psoriasis, (median age 39 [range 25-60] years; median duration of disease 17 [range 4-43] years)were studied. The median psoriasis area and severity index (PASI) [8] score was 19.8 [range 18.0-23.1]. Patients with concomitant disease, proteinuria, or haematological or biochemical measurements outside the normal range, were excluded.

All patients received 5.0 mg/kg/day CsA given in two doses. After week 12 the CsA dose was reduced 0.35 mg/kg/day at monthly intervals. The CsA dose associated with the first rise in PASI was regarded as the minimal effective CsA dose. In the event of relapse (PASI above 50% baseline value) CsA was withdrawn. In any case CsA was withdrawn after 16 months of therapy.

If there was a rise in serum creatinine of more than 30% over baseline, a rise in serum potassium above the upper limit of the normal range, or a diastolic blood pressure above 95 mmHg at two consecutive visits, CsA was reduced by about 25%. If the abnormality was not corrected within four weeks, a further reduction by 25% was made.

Whole blood CsA levels were initially checked weekly during the first month of treatment and every 4 weeks thereafter. Trough CsA concentrations (ng/ml) were measured 12-14 h after the last dose of CsA using a monoclonal antibody RIA-kit (Sandoz Ltd, Basle, Switzerland). Before initiating CsA treatment (baseline = BL), after 12 weeks of therapy and 4 weeks after complete withdrawal of CsA, renal function tests were performed using simultaneous determinations of the ^{125}I-iothalamate and ^{131}I-hippuran clearances for glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), respectively.[9]

The GFRs and ERPFs were normalized for body surface area. Clearances were expressed as ml/min/1.73 m^2. The GFR and ERPF were performed at 09.00 a.m. after the patient had fasted for at least 9 h.

Renal blood flow (RBF) was calculated by:

$$RBF = \frac{ERPF}{1\text{-haematocrit}}$$

and expressed as l/min. Blood pressure was measured in a sitting position, after 5 min rest, using a standard mercury sphygmanometer. Total renal vascular resistance (TRVR) was calculated by:

$$TRVR = \frac{MAP}{RBF} \times 80$$

and expressed as dyn s/cm^5 (MAP = Mean arterial pressure = diastolic BP + [pulse pressure/3]). (MAP is expressed in mmHg, RBF in l/min., in order to express TRVR in dynes.s.cm-5 it is neccesary to multiply MAP/RBF with 80.) Haematological and biochemical measurements were performed using standard laboratory techniques.

STATISTICAL ANALYSIS

All results are expressed as medians and ranges. For statistical analysis a two-tailed Wilcoxon signed-rank test for paired observations was used. A *P*-level of <0.05 was considered significant.

RESULTS

The results are listed in Table 1. The psoriasis improved considerably in all patients. The patients continued therapy 4-16 months, (median 11.8 months). Only four patients continued therapy for 16 months. The other four patients discontinued therapy earlier because of a relapse in psoriasis, as a result of the reduction in CsA dose. The minimal effective dose was 3.2 (2.3-4.2) mg/kg/day. Four patients had a 25% dose reduction because of side-effects, mainly a rise in serum creatinine above 30% of baseline. The renal parameters and mean renal parameters are listed in Tables 2 and 3, respectively. After 12 weeks of therapy we observed, in relation to baseline, a reduction in GFR of 17.8% (2.2-31.9%), ERPF 10.1% (7.4-27.3%), RBF 6.0% (4.1-17.5%) and an increase in TRVR 15% (NS). There was limited improvement 4 months after withdrawal of CsA, GFR -9.8% (5.5-21.5), ERPF -13.5% (3.0-32.9%), RBF -7.7% (1.6-18.1%) and TRVR +17% (NS).

Table 1 Cyclosporine therapy for psoriasis - long-term treatment results

Pat no	Age yrs	PASI BL	BP BL	CsA level	Dose red.	PASI red%	BP wk12	CsA med	CsA mo.	CsA dose	CsA end level	BP end
1	33	18.7	125/80	115	-	100	120/80	2.33	16	2.33	<25	120/80
2	34	18.0	115/65	145	K^+	62.2	110/60	4.05	4	4.05	60	115/65
3	25	21.0	135/85	135	Creat	92.3	130/90	3.71	8	2.66	50	130/90
4	60	18.1	135/90	115	-	90.6	140/90	2.50	16	2.50	60	135/90
5	41	20.0	130/80	120	-	83.0	125/85	2.60	16	2.60	50	140/90
6	45	20.5	120/80	135	Creat	92.7	135/95	2.44	13	2.44	40	125/85
7	30	23.1	120/70	110	Creat	69.0	120/70	4.25	5	4.22	85	120/70
8	44	19.0	135/85	155	-	98.9	130/80	4.30	16	2.50	35	135/80

BL, baseline; BP, bloodpressure (mmHg systolic/diastolic); CsA level, the mean CsA trough blood level (ng/ml) during the first 12 weeks of treatment; Dose red., dose reductions because of side-effects; PASI red., reduction of PASI at week 12 in comparison with baseline; CsA mo., CsA therapy in months until CsA was withdrawn; CsA med, minimal effective dose of CsA (mg/kg/day); CsA dose, CsA dose (mg/kg/day) during the last month(s) of CsA therapy; CsA end level, the mean CsA trough blood level (ng/ml) in the last month of treatment; BP end, the blood pressure in the last month of treatment (mmHg).

Table 2 Renal parameters

	Baseline				Week 12				4 months after CsA withdrawal		
Pat no	Creat	GFR	ERPF	TRVR	Creat	GFR red%	ERPF red%	TRVR % increase	Creat	GFR red%	ERPF red%	TRVR % increase
1	98	91	374	41.6	100	2.2	5.1	-1.5	100	+5.5	12.8	8.1
2	90	112	522	25.1	102	20.5	7.3	-12.4	98	21.4	23.4	7.1
3	77	117	604	24.1	100	23.9	27.3	18.0	86	5.1	24.2	16.2
4	96	83	320	50.6	96	10.8	3.1	1.0	99	13.3	2.5	-1.2
5	92	88	368	41.3	104	19.3	12.2	19.8	108	19.3	32.9	52.0
6	95	64	232	41.8	105	12.5	+7.4	44.0	104	1.6	+3.0	46.0
7	87	116	607	18.2	100	31.9	18.1	48.1	96	11.2	10.7	15.3
8	84	102	428	36.8	106	21.6	14.9	3.2	91	11.7	4.2	-8.0

Creat., serum creatinine (μmol/l); GFR, glomerular filtration rate (ml/min); ERPF, effective renal plasma flow (ml/min); TRVR, total renovascular resistance (1000 x dyn s/cm^5).

DISCUSSION

CsA is effective in psoriasis but there appears to be great variability in the minimal effective dose (range 2.33 to 4.25 mg/kg/day). In this study the median minimal effective dose was 3.2 mg/kg/day. This is comparable with values reported previously.[10,11]

Table 3. Mean renal parameters

Baseline (BL)	Week 12	4 months after CsA withdrawal
Creat 89.9	102 ($p<0.02$ vs BL)	97.8 (NS)
GFR 96.6	78.4 ($p<0.02$ vs BL)	86.8 ($p<0.05$ vs BL)
ERPF 432	378 ($p<0.05$ vs BL)	367 ($p<0.02$ vs BL)
TRVR 34.9	39.7 (NS)	41.1 (NS)

Creat., serum creatinine (μmol/l); GFR, glomerular filtration rate (ml/min); ERPF, effective renal plasma flow (ml/min); TRVR, total renovascular resistance (1000 x dyn s/cm^5); NS, not significant.

In four patients long-term treatment efficacy was limited by dose reductions necessitated by side-effects. After dose reduction, the psoriasis relapsed. This indicates that the therapeutic window for CsA therapy is small.

It is assumed that after low-dose CsA therapy for psoriasis all side-effects are reversible. However, few studies have been published in which renal function was studied with adequate GFR and ERPF measurements. Often GFR was measured after 8 or 12 weeks of therapy and not thereafter.[12] To our knowledge, only one study has been published in which the reversibility of the observed renal impairment in low-dose CsA therapy for psoriasis has been adequately studied.[13] In this study by Powles et al [13] it was shown that impairment of renal function is reversible to a large extent after long-term therapy with CsA. However, there were no baseline values for GFR and ERPF available. Therefore, an irreversible component of the renal impairment cannot be reliably excluded in their study design. Irreversible renal damage with long-term low-dose CsA therapy has been reported in patients with conditions other than skin diseases.[5,6] and morphological renal changes have been observed in psoriasis patients treated with low-dose CsA therapy for 6-18 months.[7] Morphological changes were detected in a patient treated with a dose as low as 2.5 mg/kg/day.[7]

The patients in our study were treated with an initial dose of 5 mg/kg/day. After week 12 the CsA dose was subsequently reduced until the minimal effective dose was reached, and thereafter the patients were treated with the minimal effective dose of CsA (median 3.2; range 2.33-4.25 mg/kg/day). We found considerable renal impairment, as measured by GFR and ERPF, at week 12. It is possible that, with a lower initial dose of CsA, the renal impairment would have been less.

Four months after withdrawal of CsA a sustained renal impairment could be demonstrated, in some patients as high as 20% reduction from baseline value. It is possible that renal function might improve further after this period, but until this has been investigated, CsA should be used with caution in dermatology, particularly as irreversible morphological renal changes have been observed in psoriasis patients.[7] Functional renal changes should be kept to a minimum. and an increase in serum creatinine to more than 30% over baseline should not be allowed to occur.[14]

Further studies are warranted, in which the renal side-effects during and after long-term CsA therapy are monitored.

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CHAPTER 4.

DOES FISH OIL PROTECT RENAL FUNCTION IN CYCLOSPORINE-TREATED PSORIASIS PATIENTS?

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ABSTRACT

In order to study the influence of fish oil on cyclosporine A (CsA)-induced renal dysfunction, 13 patients with psoriasis (CsA group) received CsA alone, and seven patients (CsA/EPA+DHA group) received a combination of cyclosporine A and fish oil (6 g eicosapentaenoic acid, C20:5 omega-3, and docosahexaenoic acid, C22:6 omega-3, daily) for 3 months. The glomerular filtration rate fell by 18.0 $\pm$ 9.6% in the CsA group compared with 8.7 $\pm$ 6.8% in the CsA/EPA+DHA group (mean $\pm$ SD, $P<0.05$). The effective renal plasma flow fell by 10.6 $\pm$ 8.9% in the CsA group and did not change in the CsA/EPA+DHA group ($P<0.05$). The calculated total renal vascular resistance increased by 19.8 $\pm$ 14.5% in the CsA group and did not change in the CsA/EPA+DHA group ($P<0.01$). The results of this pilot study suggest that fish oil can reduce CsA-associated renal dysfunction in psoriasis patients.

INTRODUCTION

Cyclosporine A (CsA), a fungal cyclic polypeptide, has been shown to suppress both humoral and cell-mediated immunity by affecting early steps of T-cell activation.[1] It is one of the most extensively used immunosuppressive drugs in organ transplantation at the present time.[2] Because of its immunosuppressive effects, CsA has also been used in the treatment of various apparently immune-mediated diseases such as diabetes mellitus,[3] multiple sclerosis[4] and others, with a varying degree of success. Recent studies have also shown a remarkable beneficial effect in patients with psoriasis.[5,6] The mechanism of action of CsA in psoriasis has not been fully elucidated yet. Immunosuppression of primary cytotoxic T-cell responses can play a role.[7]

One of the major problems limiting a more extensive use of CsA, however, is CsA-induced nephrotoxicity. Recent studies suggest that altered haemodynamics play an important role in CsA-induced renal dysfunction.[8] Glomerular filtration rate is reduced both in animal experiments[9] and in man[10] following CsA-administration, probably due to an increased production of thromboxane A2 (TxA2).[9] Furthermore, histological examination of the kidney after prolonged CsA-treatment reveals tubular damage.[11]

Recently, it has been shown that fish oil, containing high concentrations of the polyunsaturated fatty acids eicosapentaenoic acid (EPA, C20:5 omega-3) and docosahexaenoic acid (DHA, C22:6 omega-3), reduces CyA-nephrotoxicicty in the rat, probably by lowerig the TxA2-production.[9,12] In addition, fish oil by itself my have a limited beneficial effect on psoriasis as well.[13,14] These observations prompted us to evaluate the effects of CsA with and without fish oil in patients with severe psoriasis, in particular with respect to renal function.

STUDY POPULATION AND METHODS

Patients were selected as part of a large multicentre study (Sandoz Ltd, Basle, Switzerland, study OL 8013) to test the efficacy, safety and tolerability of CsA for induction of remission and remission maintenance in severe, recalcitrant plaque form psoriasis. Patients participating in this study were treated using CsA with either 2.5 or 5 mg/kg/day for 12 weeks.

In a pilot study in two centres (Free University Hospital, Amsterdam, and Academic Hospital, Maastricht), patients were randomized in three groups using CsA with either 2.5 or 5 mg/kg/day (together group A), or 5 mg/kg/day combined with 12 g fish oil

concentrate daily (group B) for 12 weeks. A total of 18 patients were randomized in group A and eight patients in group B.

The fish oil concentrate used was Super EPA (Pharmacaps Inc, Marlow, Buckinghamshire, UK). Each capsule of 1000 mg Super EPA provided 300 mg EPA and 200 mg DHA as their ethylesthers, and 1 IU vitamin E, resulting in a daily intake of 6 g EPA+DHA.

Whole blood CsA levels were initially checked weekly and every fornight after 1 month. Trough CsA concentrations (ng/ml) were measured 12 to 14 h after the last dose of CsA using a monoclonal antibody RIA-kit (Sandoz Ltd, Basle, Switzerland). When renal function deteriorated (increase in serum creatinine level above 30% of basline value) or when serum potassium levels rose over 5.5 mmol/l, the CsA dose was adjusted. The study design was approved by the scientific and ethical committees of the participating hospitals.

Before initiating the CsA treatment (baseline = BL) and after 12 weeks of therapy, renal function tests were performed using simultaneous determinations of the ^{125}I-iothalamate and ^{131}I-hippuran clearances for glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), respectively.[15] Clearances were expressed as ml/min 1.73 m^2. Renal blood flow (RBF) was calculated by: RBF = ERPF/(1-Ht) and expressed as l/min. Total renal vascular resistance (TRVR) was calculated by: TRVR = (MAP/RBF)80 and expressed as dynes.s/cm^{-5}. Blood pressure was measured using a standard mercury sphygmomanometer. Haematological and biochemical measurements were performed using standard laboratory techniques.

Since dietary omega-3 fatty acids are incorporated in a dose-dependent manner into plasma phospholipids,[16] we assessed compliance to the fish oil supplementation by analysis of the fatty acid composition of plasma phospholipids, described previously.[17]

A wide variation in CsA trough concentrations was found in either group. Since a correlation appears to exist between the actual blood CsA concentration and the degree of loss of renal function in the individual patient, only those patients of both groups with nearly identical CsA levels were compared.

In total, seven patients of group B were completely evaluated (CsA/EPA+DHA group)-(Table 1). One patient could not be evaluated because of non-compliance. In group A those patients selected had CsA trough levels at the time of the second renal function test comparable with the values found in the CsA/EPA+DHA group. A total of 13 patients of group A qualified for inclusion in the analysis (Table 1). Severity of psoriasis was expressed as PASI-score (=psoriasis area and severity index [18]).

Table 1
Individual CsA level (ng/ml), PASI-score, GFR and ERPF at 12 weeks. PASI-score, GFR and ERPF expressed as % of the baseline value (initial value 100%)

CsA/EPA + DHA group					CsA group				
Pat. no.	CsA	PASI	GFR	ERPF	Pat. no.	CsA	PASI	GFR	ERPF
XIX	50	0%	93.7%	97.0%	I	50	9%	89.1%	96.9%
XX	82	22%	100.4%	102.3%	XVIII	68	74%	93.2%	95.8%
					VII	73	0%	90.2%	104.9%
					XI	89	31%	68.3%	81.9%
XXI	107	4%	78.0%	95.9%	III	103	59%	85.9%	82.4%
					IX	103	8%	76.2%	81.2%
					XIV	110	14%	82.7%	78.7%
XXII	120	8%	89.1%	97.8%	VIII	114	0%	94.3%	105.2%
XXIV	120	39%	96.6%	88.1%	IV	118	47%	79.0%	92.4%
XXVI	123	16%	87.0%	107.1%	XII	123	12%	82.0%	92.1%
XXV	145	81%	93.4%	103.2%	II	135	31%	60.1%	79.8%
					XIII	138	8%	88.5%	88.3%
					VI	140	11%	76.0%	82.3%
Mean	107	24	91.2	98.8		105	23	82.0	89.4
SD	29	28	7.3	6.2		27	23	10.0	9.3

Statistical analysis

All results are expressed as mean ± standard deviation (SD). Results were analysed using a two-tailed Wilcoxon test for paired observations, and the Mann-Whitney U-test for unpaired observations, where appropriate. A P value of less then 0.05 was considered statistically significant.

RESULTS

There were no statistically significant differences between the two selected groups with respect to age and sex distribution (group A: age 38 ± 9 years, eight men and five women; group B: age 42 ± 14 years, five men and two women). Patients in group B were leaner (group A: BMI = 24.0 ± 3.1 kg m^2; group B: BMI = 21.2 ± 2.9 kg m^2, $P<0.05$). Mean concentrations of CsA in both groups were comparable (105 ± 27 ng/ml in the CsA group and 107 ± 29 ng/ml in the CsA/EPA+DHA group). As shown in

Table 1, the PASI-score in both groups, expressed as a percentage of the baseline value, showed a wide variation without any correlation between CsA levels and PASI-reduction, indicating a strong variability in susceptibility towards CsA in both groups.

Table 2
Content (in mol%) of C20:5 omega-3, C22:5 omega-3, C22:6 omega3, C18:2 omega-6 and C20:4 omega-6 fatty acids in the plasma phospholipids before baseline (BL) and after 3 months (3 mon.) of therapy in the CsA/EPA+DHA group (n=7) and the CsA group (n=13)

	CsA/EPA+DHA group		CsA group	
	BL	3 mon.	BL	3 mon.
C20:5 omega-3	1.1±0.8	6.0±1.4**	0.8±0.3	1.0±0.5
C22:5 omega-3	0.7±0.2	1.3±0.4*	0.7±0.2	0.7±0.1
C22:6 omega-3	2.7±0.9	5.0±0.9**	2.6±0.7	2.9±0.8
C18:2 omega-6	20.0±3.5	15.1±2.0**	21.7±3.1	20.2±2.6
C20:4 omega-6	6.9±1.1	6.1±0.6	7.5±0.7	7.8±1.0

Mean ±SD, paired two-tailed Wilcoxon; * = $P<0.05$ and ** = $P<0.02$, BL vs. 3 months.

No differences in overall PASI-score reduction could be observed between the two groups (Table 1). Mean blood pressure values did not change in both groups, although it was necessary to start antihypertensive medication in two patients of the CsA group.

In the analysis of the fatty acid composition of the plasma phospholipids, no changes were found between baseline and after 3 months in the CsA group. In the CsA/EPA+DHA group was a significant increase of the concentrations of C20:5 omega-3, C22:5 omega-3 and the C22:6 omega-3, with a concomitant decrease in the concentrations of C18:2 omega-6 (non-significant, $P=0.06$) and C20:4 omega-6, indicating a good compliance to the fish oil ingestion (Table 2).

In Table 1, PASI-score is expressed as a percentage of the initial score (initial score valued as 100%). GFR and ERPF values are presented, expressed as percentages of baseline values for all patients included. A great variability in susceptibility towards CsA-induced renal; dysfunction appears to exist. However, the mean CsA-induced impairment of the GFR was significantly less in the CsA/EPA+DHA group compared with the CsA group (CsA/EPA+DHA: -8.7 ± 6.8% vs. CsA: -18.0 ± 9.6%, $P<0.05$; Table 3). A comparable tendency was found for the ERPF, with a significant fall in the ERPF of the CsA group and no change in the ERPF of the CsA/EPA+DHA group (CsA/EPA+DHA: -1.2±5.7% vs. CsA: -10.6±8.9%, $P<0.05$; Table 3). As could be expected with a fall in GFR, serum creatinine levels rose in both groups (CsA/EPA+DHA: 11.8±10.3% vs. CsA: 21.5±26.3%, NS; Table 3). In both groups a fall in FF could be observed, although only significantly in the CsA group. Calculated total renal vascular resistance (TRVR) increased by 19.8 ±14.5% in the CsA group, whereas it did not change at all in the CsA/EPA+DHA group: -1.8±5.9% ($P<0.01$, Table 3).

Table 3
Renal function baseline (BL) and after 3 months (3 mon.) in the CsA/EPA+DHA group (n=7) and the CsA group (n=13)

	CsA/EPA+DHA group		CsA group	
	BL	3 mon.	BL	3 mon.
GFR	107±12	97±10*	109±15	89±13**
(ml/min 1.73 m^2)		-8.7±6.8%		-18.0±9.6%‡
ERPF	424±97	418±96	457±93	405±73**
(ml/min 1.73 m^2)		-1.2±5.7%		-10.6±8.9%‡
FF	0.26±0.03	0.24±0.04	0.24±0.03	0.22±0.03*
Serum creatinine (μmol/l)	75±17	84±18	84±10	101±19**
TRVR	10703±2507	10559±2687	9487±2459	11206±2591**
(dynes.s/cm^5)		-1.8±5.9%		19.8±14.5%‡

Mean ± SD, paired two-tailed Wilcoxon; * = $P < 0.05$ and ** = $P < 0.01$, BL *vs.* 3 months.
Mean ± SD, Mann-Whitney U-test: ‡ = $P < 0.05$ and ‡‡ = $P < 0.01$,
%delta CsA/EPA+DHA *vs.* %delta CsA.

DISCUSSION

The presented results strongly suggest an attenuation of the CsA-induced acute renal dysfunction by addition of fish oil to the diet of the patient. Our observations are supported by the recent observations of Homan van der Heide et al.,[19] who in a randomized double-blind study in renal transplant recipients observed a 20% increase in GFR when CsA was combined with fish oil over a period of 12 weeks, at least 6 months after grafting. In that study CsA trough levels remained unchanged, as did the CsA doses during the observation period.

However, a proper interpretation of our results is hampered by the fact that we performed the matching after the study was finished. By including all patients from group A with CsA levels comparable to the CsA levels in group B, we tried to prevent a bias towards a selective choice of patients. Recently, a comparable conclusion was obtained by Elzinga et al. in an experimental rat model.[9,12] In those studies, it was concluded that the beneficial effect of fish oil was mainly due to the intrarenal inhibition of TxA2-production, a potent vasoconstrictor. CsA increases the production of TxA2 in the animal model.[9]

In particular, eicosapentaenoic acid appears to be able to successfully compete with arachidonic acid in the cyclo-oxygenase pathway, thus limiting the production of TxA2.[20] However, both in the animal model and in our patients complete protection of renal function could not be achieved. Even a complete inhibition of TxA2-production in rats with a thromboxane synthetase inhibitor [21] did not return GFR to control levels, suggesting that other mechanisms are also involved in the loss renal function induced by CsA. The results of our pilot study strongly suggest that fish oil can favourably modify CsA-associated renal dysfunction in psoriasis patients. Further studies are warranted both to validate and to explain our findings.

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SUMMARY

This thesis addresses the issue of the treatment of psoriasis with single and combination therapy. At the time of initiation of these studies the immunosuppressive drug cyclosporine A had not been introduced in the clinical practice of treatment for psoriasis. In addition the potential deleterious effects of cyclosporine A were assumed not to be present when low dosages of cyclosporine A were used.

The first part of the thesis consists of a literature review of psoriasis, the possibilities for treatment, and the mode of action of cyclosporine A. Further, the indications for cyclosporine A therapy for dermatological diseases are discussed.

In the second part of the thesis, which represents clinical experience with cyclosporine A in the treatment of psoriasis and atopic dermatitis, we demonstrate that low-dose cyclosprone A is highly effective in these diseases.

Since administration of cyclosporine A has side-effects we next tried to avoid these side-effects by giving combination therapy. These experiences are represented in part III of this thesis, which shows that no combination therapy inclusive combinations of cyclosporine A with PUVA (chapter 3.1), etretinate (chapter 3.2), methotrexate (chapter 3.3) is suitable for long-term treatment of severe psoriasis because of side-effects or ineffectiveness.

The final part of this thesis (Part IV) deals with the nephrotoxic side-effects of cyclosporine A, using simple (serum creatinine concentration and Cockroft formula) or isoteric (glomerular filtration and effective renal plasma flow) measures of renal function. We showed that there is a risk for irreversible renal function loss with low-dose cyclosporine therapy (5 mg/kg/day). The renal function deteriorates less quickly when eicosapentaenoic acid (EPA, C20:5 omega-3) and docosahexaenoic acid (DHA, C22:6 omega-3) are used in combination with cyclosporine A. However, this beneficial effect is limited. Therefore, this combination therapy cannot be recommended as a standard therapy.

SAMENVATTING

In dit proefschrift wordt ingegaan op de behandeling van psoriasis. Bij aanvang van de in dit proefschrift vermelde studies was het immunosuppressivum cyclosporine A, nog niet niet beschikbaar voor behandeling van psoriasis. Destijds werd verondersteld dat behandeling met lage dosis cyclosporine A geen of slechts geringe bijwerkingen gepaard zou gaan.

Het eerste deel van het proefschrift bestaat uit een literatuur overzicht betreffende psoriasis, de behandelingsmogelijkheden bij psoriasis, effecten van cyclosporine A in de huid en indicaties voor cyclosporine A in de dermatologie.

In het tweede deel van het proefschrift wordt eigen onderzoek naar de effectiviteit van cyclosporine A bij psoriasis en constitutioneel eczeem besproken. Cyclosporine A is bij deze twee ziektebeelden bijzonder effectief.

Het gebruik van cyclosporine A wordt geremd door bijwerkingen. Om bijwerkingen te vermijden werden combinatietherapieën geprobeerd. Deze bevindingen staan vermeld in deel III van dit proefschrift. Geen van de combinatietherapieën waaronder combinaties van cyclosporine A met PUVA (hoofdstuk 3.1), etretinaat (hoofdstuk 3.2), methotrexaat (hoofdstuk 3.3) was geschikt voor toepassing in de praktijk, in verband met bijwerkingen of ineffectiviteit.

Het laatste deel van het proefschrift (Deel IV) behandeld het door cyclosporine A geinduceerde nierfunctieverlies, gebruik makend van serum kreatinine, de Cockroft formule en bepalingen van de glomerulaire filtratie snelheid en effectieve renale plasma flow. Ook bij lage dosis cyclosporine (5 mg/kg/dag) bestaat een risico op irreversibel nierfunctie verlies. De nierfunctie verslechtert tijdens cyclosporine gebruik minder snel wanneer tevens eicosapentaeenzuur (EPA, C20:5 omega-3) en docosahexaeenzuur (DHA, C22:6 omega-3) worden gebruikt. Het effect is evenwel gering en deze combinatie therapie kan daarom nog niet als standaard therapie voor dagelijks gebruik worden geadviseerd.

NAWOORD

Een proefschrift kan alleen tot stand komen wanneer men voldoende gelegenheid krijgt voor het uitvoeren van het noodzakelijke onderzoek. Bij uitvoeren van klinisch onderzoek is men bovendien afhankelijk van het aanbod aan patienten die bereid zijn aan het betreffende onderzoek deel te nemen. Een proefschrift is daarom zelden het werk van één persoon, velen helpen mee bij het recruteren van patienten en bij het creeren van voldoende tijd en gelegenheid voor uitvoering van het onderzoek.
Ik wil dan ook al diegenen bedanken die de verwezenlijking van dit proefschrift voor mij mogelijk hebben gemaakt. Met name wil ik mijn dankwoord richten tot;

Tom Stoof en ***Henk Bilo***, die mij in het door hen geinitieerde onderzoek naar de combinatie cyclosporine-visolie betrokken. Dit was de aanzet voor mijn proefschrift. Bij het opzetten en uitvoeren van de voor mijn proefschrift noodzakelijke studies hebben zij mij met raad en daad bijgestaan. Bij het verwerken van data en voor begeleiding bij publicaties is de steun van Henk Bilo van onschatbare waarde geweest.

Theo Starink die geheel belangeloos, samen met Tom Stoof, het in het AZVU geinitieerde visolie onderzoek aan mij ter uitvoering en publicatie overliet, heeft hiermee de basis voor mijn proefschrift gelegd. Uitvoering van volgend onderzoek werd door hem ondersteund en als promotor heeft hij door het geven van nuttige aanwijzingen en adviezen geholpen om mijn proefschrift vorm te geven.

Wim van de Staak, mijn opleider in de dermatologie, heeft ervoor gezorgd dat ik mij kon specialiseren tot dermatoloog waarmee ik in de gelegenheid kwam om onderzoek op het gebied van de dermatologie te doen. Hij heeft mij op het eind van de opleidingstijd geholpen om het nog lopende onderzoek ten spoedigste op een voor mij zo voordelig mogelijke wijze te volbrengen.

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Bep van Toledo en ***Ingrid Janssen*** die voor mij en mijn promotor de procedure van de promotie hebben uitgezocht en de noodzakelijke organistatie en correspondentie hebben verzorgd.

CURRICULUM VITAE

De schrijver van dit proefschrift werd op 7 juli 1959 in Goes geboren. Na het doorlopen van het VWO-b aan het Goese Lyceum ging hij studeren aan de Rijksuniversiteit Utrecht. Na een propedeusejaar in de diergeneeskunde studeerde hij van 1978 tot 1985 geneeskunde, waarna hij, in afwachting van een verdere specialisatie, als AGNIO voor de maatschap dermatologie in het Catharina ziekenhuis te Eindhoven ging werken. Na enkele maanden verhuisde hij naar Amsterdam om in het Academisch Ziekenhuis der Vrije Universiteit een opleiding tot internist te volgen, maar besloot in 1987 om deze opleiding te verruilen voor een opleiding in de dermatologie te Maastricht. Tijdens de opleiding tot dermatoloog heeft hij zitting gehad in het bestuur van de Vereniging Assistenten Dermatologie en Venereologie en werd uiteindelijk in 1990 voorzitter van deze vereniging. Tevens heeft hij namens de assistenten zitting gehad in het Concilium Dermato-venereologicum en heeft hij te Heelsum het eerste landelijke symposium voor assistenten in de dermato-venereologie georganiseerd.

In oktober 1990 vertrok hij naar de afdeling dermatologie van The University Hospital of Wales in Cardiff U.K. om daar, in de vorm van een wetenschappelijk stage, de laatste vier maanden van zijn opleiding in de dermatologie af te ronden en een functie als Clinical Research Officer te aanvaarden.

In september 1991 werd hij, in het Academisch Ziekenhuis Leiden, benoemd tot staflid in tijdelijke dienst verbonden aan de afdeling dermatologie.

De in dit proefschrift beschreven studies zijn tijdens de opleidingsperiode in Maastricht, in samenwerking met de afdeling dermatologie van het Academisch Ziekenhuis der Vrije Universiteit, uitgevoerd.

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